*Current Concepts in*
DIGITALIS THERAPY

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# DIGITALIS THERAPY

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*Current Concepts in*
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# CHAPTER I

## Introductory Remarks

THE use of digitalis marks the beginning of the modern era of cardiac therapy. Whole-leaf digitalis and the purified derivatives, the cardiac glycosides, continue as the most effective medicinal agents in the management of patients with congestive heart failure. The loss of cardiac reserve manifested by failure is the result of an imbalance between cardiac muscle strength and the work load imposed on the heart Therapy is therefore directed toward improving the function of the failing heart muscle and reducing the work load on the myocardium. The two are intertwined; affecting one influences the other Since the ultimate event in the chain leading to clinical failure occurs within the heart, the main therapeutic goal is to improve the vital function of the heart in propelling blood The digitalis drugs are the only agents known to restore compensation through such direct action on the myocardium All other measures are ancillary The need for these supplementary measures in a given case varies inversely with the efficacy of digitalis

During the last decade intensive study of the pathogenesis of one of the features of congestive heart failure — namely, edema accumulation — has focused attention on the kidney A glomerular tubular imbalance has been suggested as the critical factor in the formation of cardiac edema.[1,2] Emphasis on the

role of the kidney in increasing the cardiac load through salt and water retention has brought about a deviation from the concept of the primacy of the heart in initiating and sustaining failure. A stage has been reached at which arguments are being advanced to reassign to the heart the major role in the complex drama of congestive heart failure. The tendency to regard failure as the consequence of renal impairment has had therapeutic implications As a result therapy is sometimes based exclusively on salt manipulation achieved through various regimens of dietary salt restriction, interference with intestinal sodium absorption and the promotion of renal salt loss The mercurial diuretic and the weighing scale have been proposed as the vital implements for managing congestive heart failure [8]

Recognition of the inseparable interaction of cardiac and extracardiac factors in the pathogenesis of failure must guide therapy Translated into practice this means that digitalis is useful, with but few exceptions, during the entire course of the evolution of cardiac failure. In the early stages major reliance is placed on digitalis Measures that diminish heart work, however, are not neglected As decompensation advances and digitalis no longer overcomes the deterioration in cardiac competence, emphasis shifts to the restriction of salt intake and the promotion of salt loss In the initial phases of decompensation the aim of therapy is to improve the function of the heart for the requirements of normal life In the later phases the goal is to diminish the heart's burden and to bring it within the domain of limited cardiac performance.

As in Withering's day, the proper use of digitalis

presents many problems. Questions of when and how to administer the drug as well as how to determine the adequacy of maintenance dosage are not yet fully answered. During the past three years new data on the action of digitalis have been acquired in our laboratory. In this report some of our work and the relevant studies of others are reviewed. These are considered from five points of view: the mode of action of digitalis and the clinical indications for its use; the toxic properties common to all therapeutically active digitalis-like preparations; the changes in the toxic threshold after alterations in body electrolytes, atrial arrhythmias frequently resulting from overdosage; and a method for predicting digitalis requirement for maximum therapeutic effect before digitalization

## *CHAPTER II*

# The Action and Clinical Use of Digitalis in Heart Failure

### *Extracardiac Effects*

The rational use of digitalis requires an understanding of its action on human cardiovascular dynamics. The effectiveness of digitalis in heart failure has been attributed to direct cardiac as well as extracardiac actions. Withering was impressed with the diuretic properties of digitalis and attributed improvement to drug action on the kidneys.[4] His contemporary, John Ferriar, was the first to conclude that the essential quality of the plant was exerted on the heart. Present-day concept is in accord with Ferriar's[5] view and holds that mobilization of edema is secondary to improved cardiac function.

Recent studies with Digoxin, however, show that this glycoside has a moderate but definite diuretic action.[6] In patients without edema or with noncardiac edema a slight increase in salt and water excretion follows its administration. When normal persons are given desoxycorticosterone acetate (DOCA) and an increased salt intake until edema forms, Digoxin induces a profound diuresis comparable qualitatively and quantitatively to that observed in congestive heart failure In none of these subjects did digitalization produce alterations in renal or cardiac hemodynamics Digoxin may therefore exert a direct effect on the renal tubules Presumably, the drug depresses

sodium reabsorption by competition with a DOCA-like adrenal steroid that it resembles in chemical configuration.[6] In ordinary clinical failure the improvement that occurs with digitalization frequently precedes and at times is not associated with any significant diuresis. This suggests that if a direct renal factor is operative it is in all likelihood subsidiary to the effect of digitalis on the cardiovascular system

Is the clinical value of digitalis derived from a peripheral or central action on the cardiovascular apparatus? The reduction in venous pressure and the enhanced cardiac output after digitalization resemble the changes produced by tourniquet application or phlebotomy McMichael and Sharpey-Schafer[7] therefore concluded that digitalis acts through venoconstriction They reasoned that, by augmenting peripheral venomotor tone, digitalis lowered venous pressure, decreased venous return and lessened the overload on the heart The result was a more efficient contraction and more complete emptying of the heart

When ouabain was the glycoside tested the same observers found that in half the cases of heart failure there was a definite increase in cardiac output without associated changes in venous pressure This indicated direct stimulation of the heart[8] Others utilizing cardiac-catheterization technics found no relation between the magnitude of fall in venous pressure and the degree of increase in cardiac output Furthermore, the increased cardiac output preceded the fall in the central venous pressure[9] Similar studies in patients with isolated failure of the left ventricle demonstrated that with digitalization there was a significant increase in cardiac output and stroke volume

accompanied by a decrease in pulmonary arterial pressure. These were achieved without alterations in right-ventricle end-diastolic pressure and could not be ascribed to the action of the drug on systemic venous pressure.[10]

### *Cardiac Action*

*Effect on the heart rate* In general there are two concepts of the mode of digitalis action on the heart One school considers that restoration of compensation is an indirect effect mediated through reduction in rate, and the other attributes it to direct action upon the myocardium Mackenzie[11] and Lewis[12] ascribed the benefits to depression of atrioventricular conduction and vagal slowing of the heart rate Digitalis was therefore restricted to patients with atrial fibrillation and a rapid ventricular response. The larger number of patients whose failure was accompanied by regular rhythm frequently were not treated with digitalis Such a view is no longer tenable Extensive clinical data attest to the fact that patients with normal sinus mechanism are strikingly benefited. Experience with cardiac catheterization in failure demonstrates similar hemodynamic changes after digitalis irrespective of the underlying rhythm It is now generally believed that, with the exception of certain atrial arrhythmias, slowing of the heart rate is the result of restored compensation rather than the converse In patients with sinus rhythm digitalis may improve the clinical state before a material reduction of the heart rate Therapeutic doses slow a rapid heart only in the presence of failure When increased rate occurs without decompensation, as in the sinus

tachycardias of fever, anemia and thyrotoxicosis, digitalis is notoriously ineffective.

Atrial fibrillation may be an exception when rate reduction per se is a significant factor contributing to improvement. In patients with atrial fibrillation, who are highly susceptible to rate fluctuations, the ventricular rate reflects the state of compensation. When failure is accompanied by fibrillation with a rapid ventricular response, slowing invariably occurs with restored compensation. That rate reduction alone is a significant factor is indicated by the following observation. Occasionally, a patient with mitral stenosis and pulmonary congestion, having normal sinus rhythm, fails to improve on digitalis only to show a distinct clinical improvement with the onset of atrial fibrillation. This change for the better may take place on the same dose of digitalis if the ventricular rate after the onset of fibrillation becomes slower than it was with sinus rhythm. This apparently results from the ability of the drug in this instance to slow the ventricles when the atria are fibrillating, in contrast to its failure to do so when the rhythm is regular.

Two mechanisms are operative in slowing the heart.[13] When small doses of digitalis are administered slowing is mediated by the vagus nerve and may be abolished by atropine or exercise. As the dose is increased, extravagal factors predominate. The resting rate with small or large doses of digitalis may be the same. When the slowing is merely vagal, however, physical exertion causes exaggerated acceleration of the heart.[14] These facts account for the observation that further improvement may be achieved after more digitalis without rate alteration. In pa-

tients with atrial fibrillation rate response to exercise serves as an effective gauge to the adequacy of therapy. Such a clear-cut indicator is absent in patients with normal sinus rhythm. This is in part responsible for the belief that digitalis is effective only in patients with atrial fibrillation.

*Myocardial Action*

The major pharmacologic effect of digitalis is its direct action on the myocardium Digitalis increases the force of systolic contraction of heart muscle,[15] without alteration in the diastolic fiber size. The more forceful contraction results in more complete ventricular emptying with a rise in volume output. There is also an enhanced capacity to propel blood against increased peripheral resistance [16] At the same time the duration of systole is abbreviated, allowing greater time for both ventricular filling and heart rest.[17] The diastolic size of the heart is reduced.[18] Since oxygen consumption is a function of the initial diastolic fiber length[19] such a reduction in size diminishes the oxygen expenditure for any work output.[20] The work capacity of the heart is increased, and a greater percentage of the liberated energy, therefore, is used in the mechanical processes of shortening and development of tension The over-all result is an increase in cardiac efficiency and output The basic pattern of myocardial derangement that characterizes failure is thus reversed In other words the digitalized failing heart can do the same work with less energy (oxygen utilization) or more work with the same energy expenditure than before digitalization

*Clinical Use*

The cardinal therapeutic value of digitalis in failure is its ability to increase a deficient cardiac output. In the usual case of chronic congestive heart failure the effect on the inadequate output is continuous. In the patient with incipient failure, increase in output may occur only during brief periods of the day when demands for volume or pressure work are beyond the capacity of the myocardium. Measurable increase in the cardiac output is not an invariable end result of digitalis therapy. It occurs only in the presence of congestive heart failure.

Harrison and Leonard[21] found that, when digitalis is given to normal dogs, cardiac output is decreased by about 25 per cent. Similar reductions were observed in human and animal studies in the absence of organic heart disease. In the presence of heart disease, as manifested by cardiac enlargement, but in the absence of failure, digitalis is also ineffective in raising the output. In a third of such patients studied at rest with cardiomegaly due to cor pulmonale and hypertension, coronary-artery or valvular heart disease, digitalis decreased the cardiac output. In the remaining patients of this group output was unchanged. These results with digitalis could not be related to a previous history of congestive heart failure, to heart size or to the initial level of the cardiac output.[22] The effect of digitalis in increasing cardiac output therefore depends on the qualitative alterations in cardiac metabolism associated with failure.

Although failure is a prerequisite for the myocardial effect of digitalis, its presence does not assure

therapeutic effectiveness. The underlying process causing the failure is the critical determinant Digitalis has little if any value when the disability is due merely to a mechanical constriction within the heart, as in some cases of tight mitral stenosis with pulmonary congestion and normal sinus rhythm. Digitalis provides no relief when the congestion derives from "pericardial embarrassment of the ventricles" interfering with ventricular filling such as that occurring in cardiac tamponade or constrictive pericarditis, unless concurrent myocardial failure exists[23] Digitalis provides little benefit in the presence of active rheumatic carditis.[24,25] It has limited value in cyanotic congenital heart disease[26] Finally, digitalis affords no improvement in the majority of cases of so-called high-output failure.[27] This group is characterized by decreased peripheral arteriolar resistance Although the resting cardiac output is elevated it does not suffice for body needs altered by metabolic or mechanical factors It comprises such conditions as thyrotoxicosis, anemia, beriberi, osteitis deformans and arteriovenous fistulas

In the majority of cases of heart failure the loss of cardiac reserve is associated with a decreased cardiac output It is in this group of so-called low-output failure that the cardiac glycosides strengthen the contractile powers of the myocardium Complete or partial resolution of failure generally occurs whether the etiologic factor is hypertension, coronary-artery, arteriosclerotic or valvular heart disease and is independent of the heart rate or the underlying atrial rhythm Why digitalis is effective in failure and the

manner in which the derangement is improved remain unsolved.

*Physicochemical Basis for Digitalis Action*

Suggestions regarding the biochemical site of digitalis action are being adduced from studies on the contractile elements of muscle. According to the stimulating ideas of Szent-Gyorgyi,[21] the contractile system of muscle consists of an elongated protein conjugate, myosin, and its precipitin, polymerized actin. These two proteins are attracted by colloidal forces, but are kept apart by an atmosphere of potassium ions. The excitatory impulse depolarizes the cell membrane, which thereupon becomes permeable to cations. This permits egress of potassium ions, and diffusion follows along the gradient of their ionic concentration. The loss of cellular potassium promotes the union of the contractile proteins. These proteins adsorb adenosinetriphosphate (ATP). The resulting actomyosin-ATP complex becomes maximally discharged and folded, with a loss of energy. The enzymatic hydrolysis of ATP follows, with myosin acting as an ATP-ase and with a release of its phosphate-bond energy to recharge the contractile system and return it to a relaxed state. During the recovery phase of the cardiac cycle, catabolic processes reinvest energy into the ATP molecule so that it may serve again as the primary high-energy phosphate donor in the cell.

The complex process here outlined has been arbitrarily divided into two phases, one of energy production, during which substrate and oxygen are utilized,

and another in which the available energy is converted into mechanical work.[29,30] In low-output failure Bing[30a] has shown that left ventricular blood flow per 100 gm. of myocardium is normal. A normal pattern of aerobic oxidation continues. The glucose oxygen extraction ratio rises from a normal range of 60 to 80 per cent to an average of 100 per cent, whereas the consumption of such substrates as lactate and pyruvate remains unchanged. Furthermore, the supply of ATP is undiminished. Thus, the biochemical lesion in low-output failure appears to be lodged not in the phase of aerobic energy release but rather in the conversion of the normally available energy into useful work.[29,30] Presumably, the defect resides in the overstretched contractile elements of the muscular machine.

On the basis of clinical experience that digitalis acts mainly in low-output failure the biochemical site of its action is apparently limited to the energy-utilization phase. It may therefore be anticipated that digitalis in some manner affects either the contractile elements themselves or the concentration of intracellular potassium that mediates the contractile action.

In vitro studies are providing evidence of such action. Digitalis can accelerate the spiraling of myosin threads.[31] Digitalis compounds also speed the polymerization of actin, a stage preliminary to its union with myosin. This is true only of cardiac actin, but not of actin derived from skeletal muscle.[32] Friedman and St George[33] studied the intracellular fate of digitoxin in heart muscle and liver by means of ultracentrifugation and assay of the fractions for their digitoxin content, utilizing the duck-heart prepara-

tion. Digitoxin was not found in the mitrochondrial components where enzymes concerned with the glycolytic process of the Krebs cycle are situated but was abundantly concentrated in the area of the cell containing ATP, actin and myosin. This is in accord with the view that digitalis acts on the contractile elements of the cardiac cell. Digitalis, furthermore, affects cellular potassium concentration. Therapeutic doses are said to increase, and toxic doses to decrease, cellular potassium content.[34-36] These studies are unfolding the basis for the specificity of digitalis action in low-output failure.

*Other Uses*

Whereas the prime value of digitalis is derived from its therapeutic action on the myocardium, certain other properties find clinical use. In large doses digitalis impairs conduction in the atrioventricular junctional tissue and also prolongs the conduction recovery time of atrial muscle. These actions are utilized in atrial flutter and fibrillation. When these arrhythmias are being converted by quinidine, the atrial rate diminishes, this, together with the atropine-like effect of quinidine on the vagus, is conducive to increased facility of atrioventricular conduction with accelerated ventricular response. The increased heart rate may necessitate interruption of quinidine therapy. In such cases large doses of digitalis, by delaying atrioventricular conduction, may prevent bouts of tachycardia. In some cases of atrial flutter digitalis is directly effective in converting the arrhythmia to a more easily managed fibrillation. In addition it is the agent of choice in the treatment of paroxysmal

atrial tachycardia when simpler measures of vagal stimulation have proved unavailing.

### *Additional Clinical Comments*

As an illustration of the application of some of the principles discussed, one might comment on a frequent error that prevails in general practice. Many patients in the latter decades of life who complain of dyspnea are not helped by digitalis The drug is given because heart disease is the usual cause of shortness of breath in the elderly person. In these cases, however, the dyspnea proves to be bronchial in origin and part of the picture of pulmonary emphysema. This error could readily have been avoided because the heart under these circumstances not only is not enlarged but also may even be smaller than normal From the previous physiologic considerations it could be inferred that if the heart is not dilated, it is very unlikely that digitalis would afford any benefit

There are conditions in which certain signs and symptoms simulate heart failure but digitalis is worthless Patients may have dyspnea, rales and varied pulmonary findings owing to bronchiectasis, lung tumor or other primary respiratory lesions — manifestations that are common in heart failure and yet occur without heart disease Similarly, an enlarged liver due to Laennec's cirrhosis or neoplasm may be confused with right-sided failure. Finally, peripheral edema has numerous causes apart from heart failure In all these cases simple hemodynamic studies, such as determinations of venous pressure and circulation time, as well as x-ray examination for vascular con-

gestion of the lungs, may serve to establish the absence of heart failure

A converse example in which symptoms are lacking and yet digitalis proves of value is in the patient with hypertension who exhibits a diastolic gallop. Such a patient may not experience significant breathlessness or paroxysmal nocturnal dyspnea though the heart muscle is already in the early stages of failure that digitalis may remedy.

*Choice of Digitalizing Agent*

The varying actions of the digitalis drugs do not require different preparations. To date no fundamental differences have been found among the digitalis glycosides in their effect on the heart. The dissimilarities encountered are quantitative and related to the rapidity and degree of absorption and variability in potency and duration of action. Nevertheless, the continuing release of new digitalis preparations with claims of special efficacies causes many a physician to engage in a will-o'-the-wisp pursuit after the ideal agent. The result is that he does not master the use of a single one. The conclusion is that adequate experience with one purified digitalis glycoside in addition to digitalis leaf permits one to cope with nearly all clinical situations in which digitalis is indicated.

Powdered whole-leaf digitalis, the most widely employed preparation, gives satisfactory results in the majority of patients with early and uncomplicated congestive heart failure. When 1 2 gm is given at once, the initial effect is evident within six hours and

TABLE 1 *Properties and Mode of Usage of Commonly Employed Digitalizing Agents.*

| Agent | Route of Administration | Onset of Action | Time for Maximum Effect | Duration of Effect | Maximum Duration of Toxicity | Digitalizing Dose* | Method of Digitalization: Rapid† (Less Than 24 Hr) | Method of Digitalization: Slow (3-7 Da) | Maintenance Dose* |
|---|---|---|---|---|---|---|---|---|---|
| Digitalis leaf | Oral | 6 hr | 12–48 hr | 17 da | 1–2 wk | 1 2–2 0 gm (1 5 gm) | I, 0 6 gm. F, 0 2 gm /6 hr. | 0 3 gm /da. | 0 1–0 2 gm. (0 1 gm) |
| Gitalin (gitaligin) | Oral | — | 24–48 hr | 10–12 da | — | 3 0–10 5 mg (5 7 mg) | I, 2 5 mg F, 0 75 gm /6 hr | 1 5 mg /da. | 0 25–1 25 mg. (0 5 mg) |
| Digitoxin | I V Oral | 30 min 2 hr | 2–9 hr | 21 da + | 3 wk + | 1 3–2 0 mg (1 7 mg) | I, 0 6 mg F 0 2 mg /6 hr | 0 3 mg /da | 0 05–0 2 mg. (0 1 mg) |
| Digoxin | I V Oral | 30 min 2 hr | 4–6 hr | 4–7 da | 1–2 da | 2 0–5 0 mg (3 75 mg) | I, 2 0 mg F, 0 5 mg /6 hr | 1 5 mg /da | 0 25–1 25 mg. (0 5 mg) |
| Lanatoside C (Cedilanid) | I V Oral | 10–30 min | 2–3 hr | 2–3 da | 1 da | 1 2–3 2 mg (1 6 mg) | I V I, 1 2 mg F, 0 4 mg | — | 0 5–3 0 mg Oral |
| Ouabain | I V | 5 min | 30 min | 1–4 da | 2–6 hr. | 0 6–1 0 mg (0 7 mg) | I V I, 0 25 mg, repeat in 30 min F, 0 1 mg /30 min. | — | — |

*Numbers in parentheses are average values
†I, initial dose, F, follow-up dose

talis leaves are that it produces less nausea and does not require biologic standardization On close scrutiny, however, the value of digitoxin may not be so great as it seems. Whole-leaf digitalis preparations that are now available are carefully standardized by the various manufacturers Although the absorption of digitalis from the gastrointestinal tract varies somewhat, the clinician may still detect the effect of the dose that is absorbed and alter the amounts administered accordingly. The prolonged effect of digitoxin, sometimes exceeding three weeks after discontinuation of the drug, is a definite and serious disadvantage In the seriously ill cardiac patient the symptoms of digitoxin overdosage cannot be distinguished from increasing decompensation by the simple expedient of stopping digitalis administration for a few days

doses vary considerably and even 1.0 mg. as an initial dose may be excessive In Table 1 can be seen the speed and duration of its action

A rapidly eliminated digitalis compound is preferred in patients with advanced heart failure who are subjected to rigid salt restriction In the presence of severe decompensation it is frequently uncertain whether optimum benefit is being derived from digitalis There is no way of telling whether more digitalis will improve myocardial function except by giving more digitalis Such manipulation of dosage incurs the hazard of overdosage Furthermore, in these patients the myocardial threshold to the toxic action of

digitalis may be much reduced Even small increases in the amount of drug given may result in serious intoxication (see Chapter III, on digitalis intoxication) It is obviously desirable that the toxic action be of the briefest possible duration Digoxin, because of its rapid dissipation, is a suitable preparation for this category of patients

Digoxin is a purified glycoside of definite composition and uniform potency derived from the leaves of digitalis lanata Purity is controlled by chemical analytic methods rendering biologic standardization unnecessary It is effective both orally and intravenously Absorption from the alimentary tract is rapid and fairly complete The digitalizing dose, when given over a period of twenty-four to forty-eight hours, ranges from 2 0 to 5 0 mg In eighty-eight patients the average digitalizing and toxic dose was 3 75 and 6 0 mg, respectively[87] Thus its therapeutic toxic ratio of 63 per cent approximates the value for powdered leaf After intravenous injection, effect, as gauged by reduction of heart rate in patients with atrial fibrillation, is noted within five to ten minutes and reaches its full extent in one to two hours After ingestion digitalis action begins in one hour and maximal in six to seven hours[142,143] Oral digitalization is accomplished rapidly by giving 2 0 mg at once followed by 0 5 mg every four to six hours[144] The daily maintenance dose varies from 0 25 to 1 25 mg About 70 per cent of patients are adequately maintained with a dose of 0 75 mg or less The most effective dose associated with the least toxicity is 0 5 mg per day[145] After a single oral dose of 1 0 to 1 5 mg of Digoxin is given to patients with atrial

fibrillation and rapid heart rate, the initial tachycardia recurs in three days When full digitalization is achieved the initial level is not restored for five to seven days [142]

Some have objected to the use of Digoxin because of its rapid elimination It is argued that omission of the drug for a day or more will cause loss of digitalization. Symptoms of failure, however, are more effective than the admonition of the physician in disciplining the patient to take the drug with nearly unerring regularity Furthermore, periodic readjustment of digitalis dosage makes the physician aware of changing digitalis requirements As with digitalis purpurea, the keystone to the proper clinical use of Digoxin consists in tailoring the dosage to the specific needs of the patient.

In case of emergency for the patient with rapidly progressing acute pulmonary edema, lanatoside C (Cedilanid) or ouabain may be used Lanatoside C manifests its action within ten to thirty minutes after injection Peak effect is reached within two to three hours and persists for about sixteen to thirty-six hours,[146,147] The digitalizing dose, when used intravenously, ranges from 1 2 to 3 2 mg Digitalization can be rapidly effected by giving 1 2 mg at once followed by 0 4 mg every two hours Its prompt dissipation makes it unsuitable for oral use.

Ouabain is even more rapid in action [148] It is a pure crystalline substance derived from strophanthus gratus Ouabain is hydrolyzed in the gastrointestinal tract and is therefore restricted in use to the intravenous route Effect is initiated in five minutes and reaches its maximum within an hour The digitaliz-

ing dose ranges from 0.6 to 1.0 mg. Digitalization can be rapidly achieved by giving 0.5 mg. at once and then 0.1 mg. every thirty minutes.[149] In our experience it is safer to give two doses of 0.25 mg. within a half to one hour and then follow with 0.1 mg. Once the patient is compensated a longer-acting digitalis agent may be substituted. Apparently the full digitalizing dose of ouabain is either destroyed or eliminated within twenty-four hours. It is possible to give daily a full digitalizing dose with cumulation evident only after six to ten days. Paradoxically the suppression of tachycardia in patients with atrial fibrillation and rapid rate lasts four days.[150] Results with ouabain are usually certain, prompt and gratifying.

If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice. In the last analysis it is not the digitalis compound employed but rather facility and familiarity with any single drug that permits effective treatment of the failing heart. Whatever the drug used, best results follow when a priori notions of average dosage requirements are superseded by considerations derived from meticulous observation of the patient.

# *CHAPTER III*

## Digitalis Intoxication

### *Subjective Manifestations*

Although idiosyncrasy or hypersensitivity rarely if ever occurs, digitalis toxicity has been a problem since the introduction of this drug Little can be added to the keen observation of Withering[4] on the results of overdosage:

> [illegible] syncope and death.

All therapeutically active digitalis preparations may produce toxicity The absence of toxic properties in a digitalis body is evidence of the cardiotonic inertness of the preparation.[27] The occurrence of toxicity bears no relation to the digitalis compound employed but is conditioned by the extent of failure, the underlying etiology of the failure, the cardiac reserve, the electrolyte balance, the concurrent use of other drugs and numerous other factors

Anorexia, nausea and vomiting are among the earliest and most common subjective manifestations of digitalis overdosage. These symptoms occur whether the drug is administered orally or intravenously.[17] Emetic movements are not prevented by the extirpa-

tion of the gastrointestinal tract or by extensive afferent denervation of visceral structures The vomiting is thus of central rather than peripheral origin These symptoms may be obscured by concomitant gastrointestinal disease and may be indistinguishable from similar symptoms arising from liver and bowel congestion Advanced intoxication as evidenced by objective data sometimes occurs in the absence of all subjective indications of overdosage [38]

About 25 per cent of patients with digitalis intoxication experience either visual symptoms or dizziness The dizziness may be a true vertigo and make the ambulatory cardiac patient bedridden The visual disturbances are characterized by blurring, dancing or flickering dots before the eyes and color aberrations [40] These symptoms are trivial in comparison with the gravity of the underlying disorder Information about the presence of ocular symptoms is often not volunteered and is elicited only after careful questioning

Headache is a fairly common finding and may be the sole symptom preceding disturbances in cardiac rhythm Unusual neurologic symptoms have been observed in about 9 per cent of patients suffering from digitalis intoxication These consist of pains in the lower third of the face resembling trigeminal neuralgia associated with typical neuralgic shooting pains in the upper extremities, lower lumbar areas and calves In patients receiving large intravenous doses of the strophanthin derivative, acetyl strophanthidin, numbness and tingling of the lips, tip of nose, cheeks and ears are frequently noted In the elderly and those with advanced congestive heart failure, central nervous system findings may predominate, with

lassitude, apathy, confusion, disorientation, delirium, stupor, aphasia and at times psychotic behavior patterns. Degenerative glial and ganglionic cellular changes in the brain stem and cerebellum have been found in laboratory animals poisoned with digitalis[40]

*Cardiac Disturbances*

The most important toxic effect of digitalis is on the heart. Every form of arrhythmia and conduction disturbance has been attributed to this drug.[41] In the presence of severe myocardial damage it is a common cause of ventricular tachycardia.[42] It is probably an occasional precipitant of advanced heart block[43] These extreme reactions define the toxic potential of digitalis both as a myocardial irritant and as a depressant The interaction of these two effects makes possible the observed gamut of electrocardiographic anomalies

Irritative phenomena resulting in ectopic rhythms have been regarded as predominantly restricted to the ventricles Recent studies demonstrate the frequency and specific form of similar arrhythmias in the atria[44] This group of atrial arrhythmias and some other toxic manifestations on the heart are dealt with in a subsequent chapter

The depressant action of digitalis is mainly limited to the atrioventricular junctional tissue where the direct and indirect (vagal) actions of digitalis are synergistic. Sinoatrial and intra-atrial block and standstill of the atrium are rare. This is explained by the antagonism between the vagus nerve and direct digitalis effects on conduction recovery time in

the atria.[45] First-degree heart block is common. Bundle-branch block or intraventricular conduction impairment are unusual sequelae of overdosage, possibly owing to the absence of vagal influence on the ventricular myocardium

The earliest electrocardiographic evidence of digitalization consists of shortening of the QT interval, ST-segment scooping and inversion of the first portion of the T wave. These changes provide no index of the therapeutic adequacy of the drug nor do they permit prediction of the proximity or even the presence of toxicity Severe digitalis poisoning may occur in their absence[46]

In man, except for the gastrointestinal symptoms, ventricular extrasystoles are the most common indications of overdosage When digitalis is continued in their presence the ectopic beats assume the fixed pattern of bigeminy or coupling The occurrence of bigeminal rhythm without digitalis overindulgence generally indicates serious, frequently terminal, heart disease According to McMichael[47] the final stage of myocardial breakdown has been reached when digitalis ceases to be of benefit "In its presence it is never wise to give digitalis" This statement is valid if restricted to patients in whom bigeminy has been clearly induced by digitalis In those in whom bigeminy develops without medication adequate digitalization may abolish the arrhythmia In such cases the ventricular premature beats are expressions of congestive heart failure, inadequate coronary perfusion and myocardial anoxia, with a consequent increase in ventricular irritability Distinction between the two

son The margin of safety with all preparations is limited. For any digitalis agent approximately 60 per cent of the toxic dose is required to achieve a therapeutic effect. In this respect Digoxin, digitoxin and lanatoside C offer no advantage over digitalis leaf[57-59] An exception may be gitalin, a water-soluble amorphous mixture of glycosides extractable from digitalis purpurea. Batterman and his co-workers[59,60] claim that with gitalin only a third of the toxic dose is required for the therapeutic effect. This finding awaits confirmation. With all digitalis compounds, once toxicity emerges, a substantial percentage of the fatal dose has been administered When ventricular extrasystoles are produced in animals, from 50 to 80 per cent of the minimal lethal dose has been given[61,62]

Electrocardiographic evidence of overdosage is not always present. Advanced intoxication may exist continuously with only sporadic electrocardiographic manifestation Bigeminy in such cases can be brought on by slight exertion, deprivation of oxygen therapy, straining on the bed pan or emotional upset. The electrocardiogram at one moment shows a perfectly normal rhythm whereas a few minutes later ventricular tachycardia may dominate the picture. With advancing congestive heart failure the margin between therapeutic and toxic effects decreases In such patients, in the absence of tell-tale ventricular premature beats to arouse suspicion of overdosage, a mercurial diuresis may be fatal

Toxicity can be of prolonged duration even after digitalis is discontinued When nausea, vomiting and extrasystoles appear the practice is to stop digitalis If the symptoms persist unaltered after three or four

days or more the difficulties are attributed to the severe failure rather than to the digitalis. The resumption of digitalis under these circumstances is hazardous and further compromises a limited cardiac reserve. When critical electrolyte shifts are produced in animals digitalis toxicity usually persists for the duration of the electrolyte derangement. By this means toxicity has been prolonged forty times its usual duration[63] If the same phenomenon held true for the human being in cardiac failure, who also suffers grave disturbances in electrolyte pattern, toxicity would last many months after digitalis had been stopped This may account for the observation that small amounts of digitalis can initiate grave arrhythmias even after [illegible]

lack of well defined myocardial lesions resulting from toxic doses In animals an excess of digitalis produces areas of necrosis and fibrosis, especially in the subendocardial regions of the left ventricle[64-66] The administration of atropine diminishes and that of epinephrine increases the susceptibility of the tested animals to the pathologic lesions The underlying mechanism for the necrosis may be severe coronary vasoconstriction or a shortened period of coronary filling.[67] No morphologic changes have been noted in man Since death from digitalis finds no pathological corroboration the significance of the digitalis toxicity is often overlooked The exceptions are the rare ca[illegible] with continuous electrocardiographic tracin[illegible] just before death There are only 6 c[illegible] induced ventricular fibrillation

son. The margin of safety with all preparations is limited For any digitalis agent approximately 60 per cent of the toxic dose is required to achieve a therapeutic effect. In this respect Digoxin, digitoxin and lanatoside C offer no advantage over digitalis leaf.[57,58] An exception may be gitalin, a water-soluble amorphous mixture of glycosides extractable from digitalis purpurea. Batterman and his co-workers[59,60] claim that with gitalin only a third of the toxic dose is required for the therapeutic effect This finding awaits confirmation. With all digitalis compounds, once toxicity emerges, a substantial percentage of the fatal dose has been administered. When ventricular extrasystoles are produced in animals, from 50 to 80 per cent of the minimal lethal dose has been given[61,62]

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standing the large amount of digitalis, he experienced no subjective evidence of intoxication and exhibited only a few extrasystoles lasting for nine minutes. A

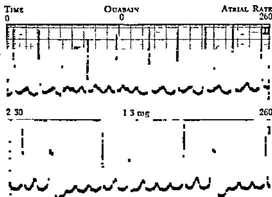



Figure 1 *Electrocardiograms in a Twenty-Year-Old Man without Organic Heart Disease but with a Spontaneous Episode of Flutter*

*A shows the tracing on maintenance digitalis therapy, and B the tracing after 1 3 mg of ouabain had been given intravenously to induce further ventricular slowing Occasional premature ventricular beats occur over a period of nine minutes*

contrasting experience is shown in Figure 2. A patient with severe right-sided and left-sided failure due to coronary-artery disease and previous anterior and posterior myocardial infarctions* had been off digitalis for about five months because of nausea and vomiting. To test his responsiveness to digitalis, he was given 1 2 mg of acetyl strophanthidin intrave-

*This case is more fully discussed by Enselberg et al.[80]

conduction" (Wolff-Parkinson-White syndrome) followed Shortly thereafter, a ventricular prefibrillatory rhythm developed. The severe intoxication lasted for about thirty minutes Two days later half the dose of acetyl strophanthidin again evoked marked toxicity.

These 2 patients demonstrate both the difficulty and the ease of producing intoxication. The underlying status of the myocardium is one of the important factors responsible for this difference. The normal, therefore, differs from the failing heart both in response to beneficial and in toxic actions of digitalis It may be that toxicity is but an extension of the therapeutic effects at the cellular level.

*Rising Incidence of Digitalis Intoxication*

With the introduction of the purified glycosides it was expected that the incidence of intoxication would diminish The patient on such maintenance therapy is assured a constant dosage because the uncontrollable variation in the potency of digitalis-leaf preparations is removed The converse, however, has been true Man [illegible]

given are that the glycosides are more toxic than leaf and that the premonitory symptoms are infrequent or absent Both these contentions are without clinical substance. The pattern of toxicity is the same irrespective of the drug employed The therapeutic-toxic ratio, the only valid way of comparing digitalis compounds, is approximately the same for nearly all these drugs

The increasing frequency of intoxication, we believe, is related to the current manner of digitalis usage and the changing methods in the management of patients with congestive heart failure.

With the purified glycosides rapid intravenous digitalization has become a common practice. As a rule this route is not justified. Digitalis intoxication more often follows intravenous medication; furthermore, the oral route permits prompt and effective achievement of the same result. A more serious problem derives from dogmatic oversimplification in dosage prescription A single-dose method for digitalizing with digitoxin has been promulgated. Patients are given 1.2 mg of digitoxin at once and are maintained on 0 2 mg daily. The administration of equivalent amounts of digitalis leaf or tincture is not possible because of the high incidence of prompt gastrointestinal upset from direct local irritant action.[73] This method has gained vogue because of its simplicity The practice is of little hazard to the ambulatory cardiac patient with early failure, especially since 1.2 mg of digitoxin, as shown by DeGraff and his associates,[58] is a subdigitalizing dose in most cases. Intoxication, however, has been repeatedly observed even with this dose [27] For the patient with serious cardiac disability the dangers multiply. Much of the toxicity reported since the introduction of the glycosides has been due to digitoxin. The validity of the single-dose method holds for the "average" cardiac patient Clinically, such patients are seldom encountered This approach creates pharmacologic rigidity for the patient with congestive heart failure Until a simple procedure has been devised for predicting digitalis require-

ments responsible practice demands empiric individualization in dosage schedule for each patient.

Another factor responsible for the increase in toxicity is the expanding life span of patients with heart disease. Antibiotics, salt restriction, surgery and application of newer physiologic principles to therapy have contributed to the lengthening of life The patients who are salvaged by these means have prolonged life expectancies with greater opportunity for even severer heart failure to develop It has already been emphasized that these sicker patients are more prone to toxicity

Perhaps the most important reason for the rise in the incidence of digitalis intoxication is the increasing dependence of treatment on electrolyte manipulation Restriction of salt ingestion and administration of mercurial diuretics, ammonium chloride, cation-exchange resins, carbonic anhydrase inhibitors and cortisone are becoming part of the therapy for failure All these measures induce changes in electrolyte metabolism and may alter the threshold of the myocardium to digitalis intoxication. Such electrolyte shifts will increasingly complicate digitalis treatment of congestive heart failure. This problem is dealt with in the next chapter.

# CHAPTER IV
## Electrolytes and Digitalis

### *Calcium*

The classical studies of Ringer[152,153] demonstrated the dependence of cardiac contraction on the electrolyte environment. In these early experiments with the perfused frog heart, it was learned that calcium and potassium ions were antagonistic in their effects on contraction. When the concentration of calcium in the perfusing medium was raised, a more vigorous systole ensued. When the concentration of potassium was raised, increased relaxation resulted In the absence of calcium the effects of potassium prevailed and the heart stopped beating in diastole On the other hand, increasing the concentration of calcium caused systolic arrest of the heart, the so-called "calcium rigor"

In the intact animal raising the serum level of calcium by intravenous injection causes bradycardia and T-wave changes. The reduction in heart rate is probably of vagal origin since it is reversed by atropine Continued administration of calcium results in ventricular fibrillation and death[154,155]

The injection of calcium salts in human beings induces bradycardia, sinus arrhythmia, shifting pacemaker, various degrees of heart block and multiple extrasystoles of large and unusual form There may also occur a flattening of the T and P waves These effects are transient.[156,157] Low levels of serum cal-

cium are associated with prolongations of the QT interval. The increased duration of electrical systole is not accompanied by a prolonged mechanical systole.[158]

Calcium and the digitalis glycosides act synergistically to increase contractility of the frog's ventricle. At any given calcium level there is an optimal concentration of potassium at which contraction is maximal. The cardiac glycosides behave as though they were substituted for a certain amount of calcium. The complex interrelations between calcium, potassium and ouabain have been expressed in a d'Ocagne [illegible][159]

shortened the survival time of the preparations.[160] This has not been corroborated in the intact animal organism. When calcium was administered to both digitalized and nondigitalized dogs no differences were detected in the electrocardiograms at the same serum levels. Furthermore, the mode of death, the lethal dose and the serum level of calcium at which fatality occurred were the same in the two groups. The conclusion drawn from this study was that calcium and digitalis were neither synergistic nor even completely additive.[161]

In digitalized patients deaths have been reported following intravenous injection of calcium.[162] The mechanism responsible for fatality is uncertain. It is possible that the failing heart may be more sensitive to the toxic action of calcium. The relation between

calcium and digitalis in patients with heart disease remains to be explored.

*Magnesium*

Magnesium salts depress the contractility of voluntary and cardiac muscle.[163-166] High serum concentrations produced by parenteral administration cause bradycardia, conduction disturbances and eventually cardiac arrest.[163] The depressant action of magnesium is not mediated by the vagus nerve since it persists after vagotomy or atropinization[165-167] Death ensues from respiratory failure

A consistent effect noted after intravenous magnesium administered to patients is a feeling of intense heat in the throat which radiates downward through the body and is associated with visible blushing.[168 169] It has been claimed that magnesium is effective in preventing ventricular tachycardia and fibrillation after large intravenous doses of mercurial diuretics[170]

The capacity of magnesium to abolish digitalis intoxication was first demonstrated by Zwillinger.[172] He successfully treated a patient with ventricular flutter after intravenous strophanthin by the intracardiac administration of magnesium. He also reported the protective action of magnesium against digitalis poisoning in frogs and dogs However, ventricular tachycardia and fibrillation can be provoked in dogs despite high concentrations in the blood.[163] Enselberg and co-workers found that 20 cc of 20 per cent solution of magnesium sulfate when given rapidly by intravenous route to cardiac patients abolished or reduced the frequency of extrasystoles due to digitalis[168] The

effect was nearly instantaneous, but of very short dura- [illegible]

The therapeutic use of magnesium for digitalis intoxication is limited by its transient action and by its occasional undesirable effects

*Potassium*

The importance of potassium ions for heart function was pointed out by physiologists near the turn of the century.[76-78] These observations were overlooked or neglected until clinical associations called attention to them Of all the ionic alterations encountered in man, those due to potassium have the most pronounced effects on the heart. One of the properties that differentiate potassium from other cations is its high rate of mobility across cell membranes.[79] This may be the basis for the critical role of potassium in muscular excitability and conductivity It appears that the migration of potassium ions links the electric phenomenon of excitation with the biochemical process of energy release essential for the mechanical event of contraction.

Changes in body potassium content when accompanied by alterations in extracellular concentration are reflected in the electrocardiogram The effects of both hyperkalemia and hypokalemia on the heart have been adequately reported

A profound relation exists between digitalis and potassium. Digitalis affects the potassium concentration of the myocardial cell There is general agreement that toxic doses of digitalis liberate potassium

from heart muscle.[80,81] Skeletal muscle also loses potassium when poisoned with digitalis [173] Digitalis sensitizes the heart to acetylcholine and vagus-nerve inhibition; these two factors have been shown to be associated with a decreased intracellular concentration of potassium [174] It may be that liberation of cellular potassium is the result of the depletion of energy-rich phosphates that occurs with digitalis overdosage [175]

No agreement exists on the effects of therapeutic doses of digitalis on cellular potassium concentration. The whole range of possibilities from no change in potassium[80,81] to cellular loss[36] and gain[34,35] has been reported. Boyer and Poindexter[35] attribute the therapeutic action of digitalis to restoration of cellular potassium and improved cellular hydration The resemblance between digitalis and adrenal steroids in chemical structure prompted the suggestion that there may also be a similarity in function in that digitalis acts to maintain potassium within the cell. Other similarities have been noted The cardiac glycosides as well as the adrenal cortical hormones protect rats, mice and cats against lethal doses of potassium and prolong the life of adrenalectomized animals.[176]

A converse relation also exists: changes in potassium concentration influence the action of digitalis. At present, data are available primarily on the toxic effect When the isolated striated muscle of a frog is treated with ouabain there is an initial rise in tension and heat production, followed in time by loss of excitability Immersing the muscle in Ringer's solution, which contains potassium, causes a reversal of toxicity [82] When rabbits are given potassium salts the lethal dose of ouabain is increased. Similarly, when

the isolated duck heart is perfused with fluid of high potassium concentration the toxic action of digitalis *is inhibited*[82] *This inhibition may be due either to* depression of myocardial irritability by potassium or to the interference with the escape of cellular potassium when the heart is exposed to large amounts of digitalis

In man potassium salts reduce or abolish ventricular extrasystoles and at times reverse paroxysms of ventricular tachycardia[84 86] The effectiveness of potassium is not contingent on the precipitating factors of the arrhythmia Castleden[177] found that epinephrine-induced ventricular premature beats were prevented when the patient was pretreated with potassium He was also successful in preventing extrasystoles occasioned by insulin hypoglycemia in a diabetic patient Sampson,[87] who first introduced potassium in the treatment of clinical arrhythmia, noted that its action is more effective when the disturbance of rhythm is caused by digitalis Other investigators have confirmed that potassium is promptly effective against many of the arrhythmias produced by digitalis[44 88,89] It has been reported that potassium salts also eliminate the symptoms of overdosage and rapidly promote a sense of well-being in patients with digitalis poisoning[88]

*Potassium Metabolism in Heart Failure*

Electrolyte and water abnormalities in congestive heart failure are due both to derangements in heart function and to the therapeutic procedures in current use

In heart failure the excretion of sodium is impaired

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plasm potassium is essential. In rats potassium deprivation induces myocardial lesions and causes death from congestive heart failure.[101]

Present-day therapy also contributes to the deranged electrolyte picture. It has been stated that electrolyte abnormalities in the serum are absent in the untreated patient.[102,103] Low-salt diets and diuretics are the chief agencies that disturb normal electrolyte equilibrium The injection of mercurial diuretics promotes the excretion of a bicarbonate-free chloride-rich urine. After administration of mercurial diuretics the urinary chloride and potassium concentrations are significantly higher and the sodium lower than their respective values in the serum. With extensive diuretic therapy hypochloremic hypokalemic alkalosis may result.[27,104] The composition of the diuretic urine and the lack of change in serum sodium and potassium levels indicate that potassium leaves while sodium enters the cellular compartment. The edematous patient who has been on rigid salt restriction for a long time is more likely to respond to mercurial agents with increased potassium diuresis[105] The patient with advanced failure is therefore more likely to experience serious losses of potassium

The protracted administration of ammonium chloride by itself may result in potassium depletion. Usually, ammonium chloride is employed to synergize the action of mercurial diuretics. The excretion of potassium is increased by such pretreatment Potassium concentration in the diuretic urine is raised by about 15 milliequiv per liter when ammonium chloride is given to enhance the action of mercurial diuretics[105]

Recently introduced methods for removing sodium

from the body exert pronounced effects on the potassium balance. Dock[182] first showed that cation-exchange resins will increase fecal elimination of gastrointestinal sodium. These resins are now widely employed in the treatment of cardiac edema. The resins in use have a greater affinity for potassium than for sodium, and unless a potassium-cycle resin is incorporated in the mixture[183,184] or adequate potassium is provided, serious deficits may occur. Hypokalemia may be encountered even when resins containing potassium are utilized.[185]

Another agent now being used as an oral diuretic is the sulfonamide derivative Diamox (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide). The sulfonamides have been found to be specific carbonic anhydrase inhibitors.[186] Such inhibition of renal carbonic anhydrase prevents the tubular secretion of hydrogen ion and its reabsorption of sodium.[187] Schwartz[188] found that sulfanilamide caused diuresis in patients with congestive failure. Diamox is from fifty to four hundred times more potent as a carbonic anhydrase inhibitor than is sulfanilamide.[189] Furthermore, it is much less toxic. These properties are finding clinical application.[190] From the standpoint of potassium, both experimental and human studies reveal that Diamox causes substantial increases in its urinary excretion.[190,191]

In patients with heart failure the underlying pathologic process and the therapeutic regimens for its management constitute the two general categories of factors that deplete both cellular and myocardial potassium. It is unknown to what extent potassium depletion contributes to the biochemical lesion and

aggravates the clinical state of congestive failure It has been demonstrated that the loss of potassium significantly affects the body's threshold to the toxic action of digitalis and may be an important cause for the rising incidence of digitalis toxicity.

## CHAPTER V

# Relation of Potassium to Digitalis Intoxication

### *Mercurial Redigitalization*

Evidence that potassium loss from the body may precipitate digitalis intoxication was first gained in a study of the postmercurial redigitalization phenomenon From twenty-four to forty-eight hours after diuresis a digitalized patient may experience nausea, vomiting, giddiness, headache and considerable weakness Electrocardiograms may demonstrate any of the changes that occur with an overdose of digitalis The mobilization of digitalis-containing edema has been implicated as the mechanism Two quantitative studies have been carried out to date Miller[192] determined the amount of digitalis in ascitic and pleural fluid by means of the Hatcher cat assay technic In digitalized patients with heart failure he found the tremendous concentration of 0 46 to 0 9 cat units per 100 cc of edema Schnitker and Levine[106] utilized the frog assay method and also noted significant quantities of drug in the extravascular fluid accumulations of digitalized patients They presumed that as much as 0 1 gm of digitalis leaf or equivalents may be present in a liter of edema It was their conclusion that the postmercurial manifestations were due to the [illegible]

dosage after diuresis

If the explanation is valid, the administration of an extra amount of digitalis, without any diuretics, to patients who tend to develop this syndrome should precipitate toxicity The additional amount required would be predictable from the size of the diuresis (assuming that a liter of edema contains as much as 0 1 gm. of digitalis bodies). When a dose of digitalis is given equivalent to the maximum amount presumed mobilized no toxicity follows. If, for example, a patient who experiences postmercurial redigitalizations with diuresis of about 1500 cc. receives in addition to his maintenance dose 0 15 to 0 3 gm of digitalis leaf, no toxicity is produced. There is a further objection to this theory If digitalis-laden edema is the causative factor, the onset of the syndrome should relate to the magnitude of the diuresis Schnitker and Levine[106] observed no such relation Direct evidence of the absence of digitalis glycosides in edema fluid has been provided in a recent study by the micro-assay technic utilizing the embryonic duck-heart preparation [193] These investigators found that edema fluid removed from 8 patients digitalized with digitoxin revealed a maximal digitoxin content of 20 micrograms per liter of edema. In half the patients no digitoxin was detected Even massive diuresis, therefore, could not mobilize sufficient digitalis to account for the postdiuretic intoxication phenomena.

A mechanism [illegible] must operate to chan[illegible] tion of some of [illegible] enon suggests another explanation The patients who exhibit such postmercurial difficulties invariably have advanced congestive failure They have been main-

tained on rigid salt restriction and are usually receiving ammonium chloride to improve the response to mercurials.[106] These are the patients who are likely to excrete substantial quantities of potassium in response to diuretics. It may be that the heart's threshold to the toxic properties of digitalis is reduced by potassium depletion, as is true in isolated heart preparations[83]

If potassium loss is responsible for the toxicity, potassium administration should abolish it. This is indeed the case The action of potassium on the post-diuretic symptoms and signs is no different from its action in stopping other manifestations of digitalis poisoning After the ingestion of potassium chloride the first effects are noted within twenty to thirty minutes Peak action occurs in one to three hours, at the time when the highest serum level is achieved Dissipation of effect follows within four to eight hours. Occasionally, digitalis-induced arrhythmias are permanently eliminated, usually there is a recurrence within the above-indicated time interval after a single dose of potassium.

The nonspecificity and transiency of the potassium effect would lead one to conclude that the action of potassium is pharmacologically in the nature of a depression of myocardial irritability rather than the result of a correction of deficits resulting from the diuresis This conclusion is contradicted by the following experience When a patient who consistently develops redigitalization is given potassium during the diuresis the later occurrence of symptoms and signs is prevented Since the duration of the effect of potassium is about eight hours, whereas toxicity usually

Mercaptomerin, which had been supplemented by ammonium chloride This time the response to 1 2 mg of acetyl strophanthidin was qualitatively different (Fig 3B). Within 5 minutes of the injection multifocal ventricular premature beats appeared, with runs of bigeminy and trigeminy One hour after the strophanthidin the patient experienced nausea and vomiting. Toxicity persisted for about 90 minutes, whereas the therapeutic slowing continued for 4 hours Study of the potassium balance revealed a loss of 83 milliequiv after the ammonium chloride and mercaptomerin, without any significant changes in the serum potassium concentration.

A R, a 20-year-old woman with mitral stenosis, had normal sinus rhythm and right-sided and left-sided failure. On 2 occasions, 1 month apart, she was digitalized with small fractional doses of ouabain to end points of mild toxicity. Each digitalization followed a mercurial-induced diuresis that resulted in excretion of significant quantities of potassium (Table 2) The atrial mechanisms at the time of the 2 tests were different, and yet the requirements of ouabain were nearly the same (Fig 4A) With 0 6 mg and 0 7 mg of ouabain nausea, vomiting, changing atrial pacemakers and rare ventricular premature beats developed The arrhythmias persisted for several hours

When ouabain was given in an identical manner but after a positive potassium balance, achieved by the ingestion of 7.5 mg of potassium chloride daily for 10 days, the dose for toxicity was nearly doubled (Fig. 4B) This occurred despite a 20 per cent reduction in weight After 1 2 mg of the drug the patient exhibited the same toxic end point as previously, and with a total dose of 1 3 mg she experienced nausea and vomiting Ventricular extrasystoles were not observed The changing auricular pacemaker persisted for only 1 hour

Two patients in similar studies who did not sustain losses of potassium after diuresis showed no changes in threshold to the action of acetyl strophanthidin [107]

The postmercurial redigitalization phenomenon may be defined as a state of increased myocardial sensitivity to the toxic properties of digitalis resulting from a negative potassium balance precipitated by diuretic

TABLE 2. *Successive Digitalization with Fractional Doses of Ouabain to the Earliest Electrocardiographic Evidence of Intoxication* *

| DATE | DRUG | POTASSIUM BALANCE | POTASSIUM SERUM | BODY WEIGHT | AMOUNT OF OUABAIN FOR TOXICITY | DURATION OF TOXICITY |
|---|---|---|---|---|---|---|
| | | *milliequiv* | *milliequiv /liter* | *kg.* | *mg* | *hr.* |
| May 3 | Mercaptomerin (2 cc ) | −100 | 5 1 | 44 | 0 7 | 4 |
| June 3 | Mercaptomerin (2 cc ) | − 70 | 3 6 | 39 | 0 6 | 3 |
| June 13 | Potassium chloride (7 5 gm per day for 10 days) | +210 | 5 2 | 35 | 1 2 | 1 |

*On May 3 and June 3 ouabain administered 24 hr after the production of negative potassium balance by means of mercurial-induced diuresis Serum potassium values on morning of digitalizations not altered by previous mercury diuresis On June 13 ouabain again given, this time after ten days of potassium supplementation and positive balance (see also Figures 44 and B) *Note increased tolerance to ouabain afforded by administration of potassium*

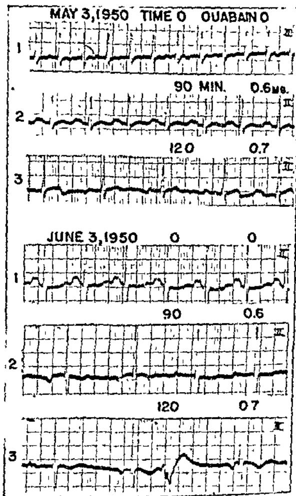



FIGURE 4A *Electrocardiograms in A R*

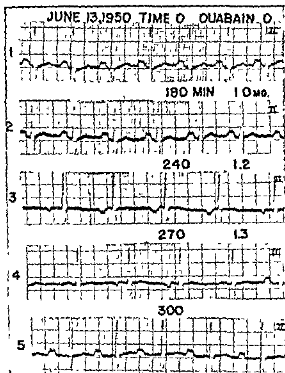



FIGURE 4B Electrocardiograms in A R

*A and B represent different occasions when ouabain was given intravenously In each a prior mercurial injection had been followed by substantial diuresis and potassium excretion (Table 2) A1 are control tracings, 2 and 3 were obtained thirty minutes after 0 6 and 0 7 mg ouabain Nausea and vomiting followed both digitalizations In B, after 7.5 gm potassium chloride daily for ten days ouabain was again administered with same dosage schedule as previously Toxic*

*protective action of potassium )*

therapy. In its presence digitalis should be discontinued and potassium administered by mouth until the evidence of overdosage disappears Serious disturbances of rhythm and even death will be prevented if diuretics are withheld when the patient gives any evidence of digitalis intoxication.

*Potassium Depletion Through Means Other than Mercurial Diuretics*

Losses of potassium, irrespective of cause, potentiate the toxic action of digitalis. Both desoxycorticosterone acetate and cortisone may produce negative potassium balance and alter the threshold of the heart to digitalis.[44,107] We have observed a case in which postmercurial redigitalization developed only after cortisone had been started. Symptoms and signs were controlled by oral potassium supplementation. Marked disturbances of rhythm may result from small doses of digitalis when patients have sustained chronic potassium depletion through either the renal or the gastrointestinal route. In these patients, especially when the serum potassium level is depressed, even small amounts of digitalis can prove fatal.

Generally, there is no reliable correlation between serum potassium concentration and digitalis requirement. The increased sensitivity that at times follows diuresis is not reflected by the serum level The serum potassium value is usually normal in the presence of digitalis intoxication. When the manifestations of overdosage are reversed with potassium there is no significant or sustained rise of the serum potassium concentration A relation, however, exists between body potassium balance and the heart's sensitivity

to digitalis This sensitivity increases with a negative balance and decreases with a positive one.

There is one exceptional circumstance where lowering of the serum potassium concentration without reducing body stores sensitizes the myocardium to the toxic action of digitalis. The intravenous administration of glucose and insulin to digitalized patients and animals may provoke digitalis-like arrhythmias.[107,194] Within five to ten minutes after injection there is a fall in the serum potassium level The hypokalemia is transient and is caused by the withdrawal of extracellular potassium necessary for the deposition of glycogen in cellular depots[195] The arrhythmia is closely correlated in onset and termination with the alterations in the serum potassium values

It is possible that in this special example cellular deficits of potassium are also involved in the fundamental mechanism The cellular compartment is not a single homogeneous reservoir Factors governing concentration of the bulk ions no doubt are differentiated to subserve specific tissue function, so that concentration will vary from tissue to tissue with changes in internal and external environment The internal shifts in this case might increase the potassium in tissues where glycogen is being deposited while decreasing it in the myocardium The sharp gradient in potassium concentration existing between cells and interstitial fluid may require cellular oxidative energy for its maintenance It can be postulated, therefore, that in the presence of tissue anoxia or interference with cellular nutrition minor fluctuations in extracellular potassium concentration critically affect the concentration ratio between the two compartments The

patient with congestive heart failure thus may be predisposed to release myocardial potassium when the serum level is abruptly lowered.

*Animal Hemodialysis*

The studies cited above do not establish with finality a relation between the myocardial threshold to digitalis toxicity and the potassium balance of the body. In all cases multiple and complex electrolyte changes in addition to those due to potassium were either induced or present at the time of the digitalization. This limitation can be overcome by the use of the artificial kidney Hemodialysis makes possible selective alterations of individual ions while controlling other variables. Furthermore, the availability of acetyl strophanthidin* as the digitalizing agent permits numerous discrete digitalizations to identical end points in the course of a single day The combination of these methods enables one to effect biologic titration of digitalis requirement while body potassium is being increased or decreased.[63,108]

The relation of digitalis to potassium was investigated in 11 dogs by means of the artificial kidney and acetyl strophanthidin During this study, which consisted of four phases spaced one to two weeks apart, 178 individual digitalizations were carried out to end points of ventricular tachycardia. In the first phase 5 separate digitalizations were accomplished, with fractional doses of acetyl strophanthidin at two-hour intervals. During the second phase the digitalizations were repeated while the dog was being hemodialyzed against a normal bath, with electrolytes in the dialysate

*Kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

ABLE 3. *Dosages Required to Produce Ventricular Tachycardia in Dogs in 178 Digitalizations before and during Hemodialysis, with Alterations in Body Potassium* *

| Period | No of Digitalizations | Average Serum Potassium | Dose of Acetyl Strophanthidin Required for Toxicity |
|---|---|---|---|
| | | *milliequiv /liter* | *mg.* |
| Before dialysis | 62 | 4.1 | 0.74 |
| During dialysis, with normal bath potassium concentration (4.0 milliequiv per liter) | 55 | 4.3 | 0.47 |
| During dialysis, with low bath potassium concentration (0.1 milliequiv per liter) | 19 | 2.1† | 0.19 |
| During dialysis, with high bath potassium concentration (8.0 milliequiv per liter) | 22 | 7.0 | 1.15 |

*Note the large dose of acetyl strophanthidin (1.15 mg.) needed when potassium is high and the small dose *(0.19 mg.) when potassium is low.*
†Extraction, 25 milliequiv.

adjusted to their respective *serum concentrations*. The third procedure was limited to extensive potassium extractions by hemodialyzing against a bath without potassium. The final phase, the titration dialysis, again consisted of 5 digitalizations, 1 carried out before and 4 during the dialysis. Of the 4 digitalizations on the artificial kidney, 1 followed two hours of potassium extraction, another followed the addition of potassium, and 2 were accomplished while the potassium *was maintained at a normal value*

The data indicated that the quantity of acetyl strophanthidin necessary for toxicity remained constant if the dogs were digitalized every two hours With the start of hemodialysis there was a reduction in the dose needed to produce ventricular tachycardia Thereafter, irrespective of the duration of dialysis, the dose remained constant as long as no electrolyte alterations were induced During the potassium extraction phase, which lasted over four hours, the serum level was lowered to about 1.9 milliequiv and an average of 48 milliequiv. was removed from the body Although specific electrocardiographic changes involving auricular and ventricular complexes were produced, no arrhythmias or conduction disturbances resulted.[196]

When body potassium was increased during the titration dialysis, the dose of acetyl strophanthidin for toxicity rose to 240 per cent of the normal dialysis requirements Toxicity lasted a few seconds. Atrial standstill was usually produced prior to disturbance in the ventricular rhythm. When massive doses were administered interventricular block and cardiac arrest rather than ventricular tachycardia followed [151,196]

When digitalization was carried out after the removal of potassium striking qualitative and quantitative changes ensued During the titration dialysis the serum potassium was lowered to 2 1 milliequiv., and 25 milliequiv was removed (or about half the amount eliminated from the body during the longer extraction phase) The dose of acetyl strophanthidin necessary for toxicity was lowered by 60 per cent compared with digitalizations during normal dialysis (Table 3). The reduction in the amount of acetyl was consistently greater than 40 per cent.

There was also a significant prolongation of the duration of toxicity Without changes in body potassium ventricular tachycardia persisted for a maximum of fifteen minutes When the potassium was lowered toxicity lasted several hours A further difference was the emergence of multifocal premature beats, bigeminy and bidirectional ventricular tachycardia (Fig 5). Hitherto, such rhythms have not been induced with digitalis in the intact mammalian heart in situ [47]

It can be concluded that dogs depleted of potassium respond to digitalis in a manner similar to that observed in the cardiac patient in failure there is a significant reduction in the dose that will cause intoxication, toxicity once produced is of prolonged duration, and there is an appearance of multifocal ventricular rhythms

*Human Hemodialysis*

Patients with renal shutdown are improved by hemodialysis In some cases the procedure may be lifesaving If the relation between digitalis and potassium described in dogs holds for human beings

*Clinical Problems*

Digitalis intoxication may simulate conditions that require digitalis for control, and, conversely, arrhythmias caused by various agencies besides digitalis may resemble digitalis intoxication. At times, prompt recognition of the underlying nature of the cardiac disturbance may be lifesaving. The following cases illustrate these points.

A.N., a 47-year-old man with mitral stenosis and regurgitation, for 8 years had had right-sided and left-sided failure with atrial fibrillation. During the year before admission he began to experience angina-like chest pain and became completely incapacitated. At the time of entry to the Peter Bent Brigham Hospital he was in severe failure, with marked orthopnea, chronic pulmonary congestion, ascites and ++++ peripheral edema. Shortly after admission digitalis was stopped because of the development of a nodal tachycardia. His condition deteriorated rapidly. To assess the degree of digitalization, a digitalis tolerance test (described in Chapter VII) was carried out, indicating that he would benefit from full digitalization. This was accomplished within 24 hours. Thereafter, improvement was progressive. Within a 2-week period he lost 14 kg. of edema.

His improved status permitted the performance of valvuloplasty. Two days after the operation, notwithstanding increasing doses of digitalis, his heart rate accelerated and became regular. At this time he was cyanotic, moist rales were present at the lung bases, the systolic blood pressure was less than 90, and he appeared in peripheral vascular collapse. The idea of giving more digitalis was entertained. Since nodal tachycardias may be caused by digitalis overdosage, the final decision was to administer potassium. After 30 milliequiv. of potassium chloride had been given by vein the rhythm reverted to atrial fibrillation (Fig. 6). The patient's immediate status improved. The next day, without receiving any digitalis he was nauseated and vomited, and the electrocardiogram exhibited a trigeminal rhythm.

The regularization of the ventricular response in

rapid (Fig 7). At the end of 1 hour his blood pressure rose to 124/78, and he began to have a copious diuresis Thereafter, recovery was continuous and uneventful. A blood sample drawn before therapy revealed a potassium concentration of 7.5 milliequiv. per liter, corroborating the impression of hyperkalemia.

These patients illustrate two contrasting situations. Superficial examination of A N. would have led one to give more digitalis. The patient, indeed, was showing an increasing heart rate, and the general circulatory state was deteriorating Further digitalis might very well have proved lethal. The regularity of the rapid ventricular response in a previously fibrillating patient was the special feature that suggested overdigitalization For that reason potassium was given and was effective

In E M the lack of P waves again led the attending staff to the diagnosis of nodal rhythm caused by an overdose of digitalis The administration of potassium was considered However, the possibility of digitalis intoxication was dismissed for two reasons· in human beings digitalis intoxication does not cause intraventricular-conduction impairment, and when complete atrioventricular dissociation or nodal rhythm results from an overdose of digitalis, the ventricular response is usually regular When it is irregular, interference from sporadic conduction of the atrial impulse is evident.

A slow irregular ventricular rhythm with intraventricular block and atrial paralysis strongly suggests potassium poisoning This is to be considered even in the absence of the characteristic changes in the T contour Advanced hyperkalemia may be present without peaked T waves[110] In E M. the rapid

infusion of bank blood under pressure may have produced hemolysis and thus provided an exogenous source of potassium. The control of the hyperkalemic effects on the heart by the combination of hypertonic sodium solution, glucose and insulin permitted the kidneys to excrete the excess potassium without further deleterious sequelae.

# CHAPTER VI

## Paroxysmal Atrial Tachycardia with Block

The relation between the potassium balance of the body and the toxic action of digitalis called attention to paroxysmal atrial tachycardia with block. This *arrhythmia frequently resulted from either an absolute* overdose of digitalis or a relative overdose conditioned by a changed cardiac threshold. Study corroborated and amplified the interaction of potassium and digitalis [44]

Digitalis in toxic amounts has been reported to produce the whole gamut of cardiac arrhythmias encountered clinically [111] Disturbances in ventricular rhythm are well recognized consequences of digitalis intoxication. Abnormal atrial mechanisms, however, are regarded as rare and nonspecific In our experience paroxysmal atrial tachycardia with block is a common, serious and specific clinical entity that usually results from digitalis intoxication [112]

### *Electrocardiographic Features*

While the presence of paroxysmal tachycardia with block can be suspected on purely clinical grounds, its identification is not possible without an electrocardiogram It is a hybrid arrhythmia partaking of the characteristics of both atrial tachycardia and flutter The atrial rate varies from 120 to 250, the usual rate range being between 150 and 190. The onset and offset are gradual and sequential. Unlike untreated

flutter, in which 2:1 block is the rule,[113] only 30 per cent of cases of paroxysmal atrial tachycardia with block show such a response.[112] In the remainder the degree of block varies and is often inconstant. The Wenckebach type of conduction is a common finding. Consecutive PR intervals may differ significantly in

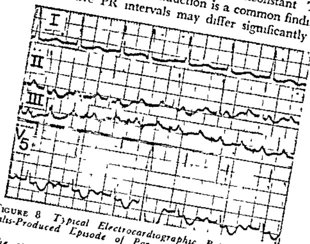



FIGURE 8. *Typical Electrocardiographic Pattern of Digitalis-Produced Episode of Paroxysmal Tachycardia with Block*

*The atrial rate is 190. Ventricular response is variable. P waves are upright in the limb leads. Note iso-electric base line in Leads 2 and 3 and ventricular premature beat in Lead $V_5$.*

duration, giving the impression of complete atrioventricular block. When the evolution of the arrhythmia is continuously observed a 1:1 atrioventricular response invariably precedes the emergence of the block. The impaired conduction is increased by vagal stimulation and diminished or abolished by atropine or exercise.

The P waves, when discernible, are upright in Leads 1, 2 and 3. They may be indistinguishable from the P waves originating in the sinus node, but generally differ in contour and amplitude. In some cases the P wave is notched or peaked and of great size. In others it is extremely diminutive, barely ruffling the base line. The PR interval may not be constant; those incorporating a QRS complex are at times of shorter duration. Unlike flutter, in which the base line is in continuous motion, in this arrhythmia an iso-electric interval separates the atrial complexes (Fig. 8).

Evidence of digitalization is usually present. The ST segment may be depressed, with inversion of the first portion of the T wave and QT-interval shortening. In addition ventricular premature beats are observed in most patients. These may occur singly or assume bigeminal patterns and at times give way to brief or prolonged runs of unidirectional or bidirectional ventricular tachycardia.

*Experimental Studies*

In dogs paroxysmal atrial tachycardia with block has been produced by an overdose of acetyl strophanthidin and by the removal of potassium from the digitalized animal. The administration of glucose and insulin to dogs who have been digitalized evokes atrial tachycardias. The phases in the emergence of these arrhythmias are similar to those observed in clinical cases.[197]

If paroxysmal atrial tachycardia with block, as observed in the cardiac patients, is caused by digitalis, it should be possible to demonstrate the following: the production of this arrhythmia by digitalis when the

intervention of other factors is excluded; the precipitation of paroxysmal atrial tachycardia with block in the digitalized patient by the loss of potassium from the body; the abolition of paroxysmal atrial tachycardia with block by the administration of potassium and the failure to abolish auricular arrhythmias, including paroxysmal atrial tachycardia with block, when digitalis is not a factor in their genesis

*Production by digitalis* Heyl[114] was the first to demonstrate that digitalis was a causative factor of this arrhythmia On three separate occasions he was able to induce paroxysmal atrial tachycardia with block in a patient with congestive heart failure by the administration of digitalis leaf. When the drug was discontinued normal sinus rhythm was re-established The arrhythmia exhibited all the essential features described above (Fig 8) The role of digitalis and quinidine was later also suggested by Decherd, Herrmann and Schwab[115] on the basis of a study of 40 patients Of this group, 33 had received digitalis, and in 23 the amounts were regarded as excessive by the authors In a study of 1247 patients with acute myocardial infarctions, Askey[117] observed 5 with supraventricular tachycardia Two of the patients showed the typical features of paroxysmal atrial tachycardia with block In these 2 and in 2 others digitalis was implicated in production of the arrhythmia

In these clinical experiences many factors were operating, and the role of digitalis was conjectural If a relation between digitalis and paroxysmal atrial tachycardia with block exists it is necessary to demonstrate its operation without the intervention of other important variables This was made possible by the use

of acetyl strophanthidin, which permits digitalization in the course of a few minutes. To date we have observed 3 patients in whom paroxysmal atrial tachycardia with block promptly followed the intravenous administration of acetyl strophanthidin. No other drugs were utilized The maximum interval for the emergence of the arrhythmia was twelve minutes and its development was a gradual sequential process identical in the 3 patients

There were roughly four phases in this development The first consisted of an increase in atrial rate frequently associated with a slight or prominent alteration in the contour and magnitude of the P wave but not in its direction. This represented the usurpation of pace-setting function by a more excitable ectopic focus. A gradual acceleration of the atrial mechanism followed, with a continuation of a 1:1 ventricular response. The third phase consisted of migration of the P waves with increasing atrioventricular block Lastly, when the rate had reached a critical level, 2:1 or greater or less degrees of atrioventricular block developed (Fig 9) The critical rate at which block ensued differed from patient to patient and in any one patient under varying circumstances The experience in these 3 patients clearly indicates the association with digitalis

*Production by potassium removal.* In digitalized patients the loss of body potassium may have the same effect as the administration of additional digitalis In the study with the artificial kidney discussed above, 7 of the digitalized patients gave evidence of intoxication during the removal of potassium by hemodialysis. In 2 of these patients paroxysmal atrial tachycardia

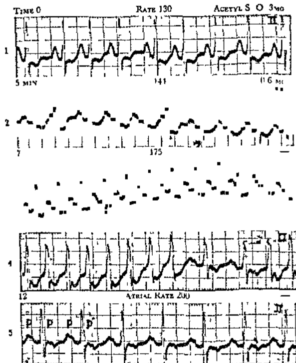



FIGURE 9 *Production of Paroxysmal Atrial Tachycardia with Block by the Administration of Acetyl Strophanthidin in a Digitalized Patient*

*The earliest event consists of a change in pacemaker and acceleration of rate* (2) *This is followed by continued in-*

rate of 200 (4)

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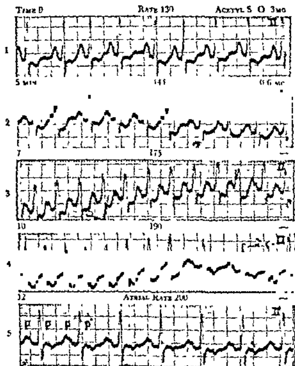



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*The earliest event consists of a change in pacemaker and acceleration of rate (2). This is followed by continued in-*

*rate of 200 (5).*

with block developed, and in a third its maturation was stopped by potassium administration. The evolution of the arrhythmia was gradual and followed the same sequence as in the patients who received acetyl strophanthidin. A change in pacemaker was the first harbinger of the tachycardia This was followed by acceleration of rate and increasing atrioventricular-conduction impairment, which finally resulted in second-degree heart block (Fig 10). In 2 of the 3 patients other evidence of digitalis intoxication also developed The reduction in the serum potassium concentration at which the arrhythmias began averaged 1 milliequiv. per liter. In all 3 patients, however, the values were above 3 5 milliequiv, and in 1 it was 5 6 milliequiv. per liter. Elevation of the serum potassium level to its value before the arrhythmia did not promptly reverse the tachycardia

*Abolition by potassium administration.* When paroxysmal atrial tachycardia with block is caused by digitalis potassium is rapidly effective in restoring a normal mechanism (Fig 11) In 10 episodes induced [illegible] iv. (1.5 to [illegible] orally or [illegible] Table 5).

The process of reversion of the arrhythmia by potassium was a chronologic mirror image of the stage in its evolution The first change consisted of a slight slowing of the ectopic focus, with establishment of a 1:1 atrioventricular response. This was associated with a sudden increase in ventricular rate and with aggravation of symptoms of dyspnea and palpitation A diminution in atrioventricular block followed, with visible migration of the P waves and continuous re-

duction in the heart rate. An abrupt change in the P-wave contour then resulted in the re-establishment

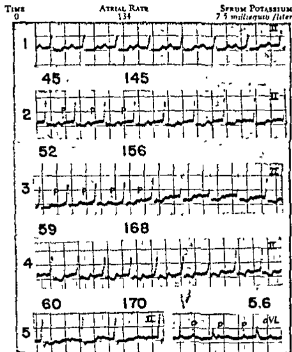



Figure 10 *Production of Paroxysmal Atrial Tachycardia with Block by the Removal of Potassium in a Digitalized Uremic Patient*

*Phases in development are similar to those when the arrhythmia is produced by an overdose of digitalis*

of a sinus rhythm[44] (Fig 11)

Potassium is ineffective in the absence of a back-

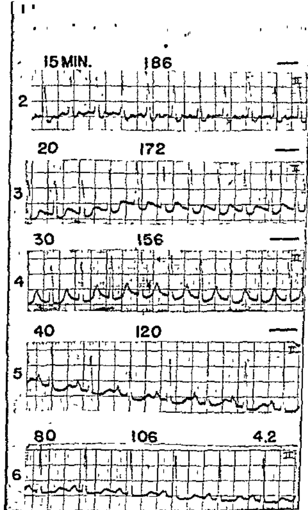



FIGURE 11. *Abolition of Paroxysmal Atrial Tachycardia with Block by the Administration of Potassium*

*With slowing of atrial rate 1:1 atrioventricular response develops, with paradoxic ventricular acceleration (2). Atrioventricular block diminishes with decrease in atrial rate (3, 4, 5). Finally, abrupt change in contour of P wave with reconstitution of normal sinus rhythm. See Figures 9 and 10*

ground of digitalis intoxication. This is true even if the mechanism is paroxysmal atrial tachycardia with block. In 6 cases of atrial arrhythmias not due to digitalis, 3 of which were paroxysmal tachycardia with block, the administration of 40 to 200 milliequiv. (3 0 to 15 0 gm ) of potassium chloride did not alter the atrial mechanism Potassium was ineffective even though hyperkalemia was produced in 3 of the 6 patients (Table 5)

It can therefore be concluded that an overdose of digitalis affects atria as well as ventricles The atrial manifestations of advanced digitalis intoxication assume the specific form of paroxysmal tachycardia with block The laws relating potassium to the myocardial threshold for digitalis toxicity operate in this arrhythmia as in other cases of digitalis poisoning

*Clinical Studies*

*Incidence and predisposing factors* In a period of eleven years at the Peter Bent Brigham Hospital 66 episodes of paroxysmal atrial tachycardia with block were observed in 51 patients [112] Half the episodes occurred during the past three years In 12 of the bouts of tachycardia digitalis was not a factor In the remainder, all of which were associated with digitalis, the evidence suggested either absolute or relative overdosage (Table 6) Of the 54 episodes 36 were due to a distinct overdose, 8 were precipitated by a massive mercurial diuresis while the patients were on maintenance digitalis therapy, and in 10 others a variety of factors involved were believed to have sensitized the patients to digitalis toxicity In 6 of these substantial losses of potassium, resulting either from intrinsic

TABLE 5 *Effect of Potassium Administration on Atrial Arrhythmias.**

| Cause of Arrhythmia | No of Patients | Episodes of Arrhythmia | Type of Arrhythmia | Potassium Given | Results of Potassium Administration | |
|---|---|---|---|---|---|---|
| | | | | | Hyper-kalemia | Reversion of Arrhythmia |
| | | | | *milliequiv.* | *no. of cases* | *no. of cases* |
| Digitalis-induced | 6 | 10 | Paroxysmal atrial tachycardia with block | 20-100 | 0 | 10 |
| "Spontaneous" | 6 | 6 | Paroxysmal atrial tachycardia with block (3 cases)<br>Flutter (2 cases)<br>Nodal tachycardia (1 case) | 40-200 | 3 | 0 |

*Note that potassium reverses only arrhythmias produced by digitalis.

renal lesions or from extraction by hemodialysis, were the factors In 3 of the remaining 4 the administration of cortisone, insulin or calcium precipitated the arrhythmia, whereas in the fourth the predisposing factor appeared to be a 100-pound weight loss. Thus, in slightly over 80 per cent of the episodes, digitalis was involved in the emergence of paroxysmal atrial tachycardia with block In all patients in whom digitalis was implicated the arrhythmia ceased when the drug was discontinued.

The data indicate a continuing increase in the observed incidence of paroxysmal atrial tachycardia with block. Although the heightened awareness and recognition of this mechanism is a factor, in all likelihood an actual rise in frequency has occurred. No doubt the conditions discussed above, at the beginning of this section, as responsible for the augmented incidence of digitalis intoxication also account for the increased incidence of tachycardia with block. An additional reason may be that potassium loss favors the development of this arrhythmia Of the 7 patients exhibiting digitalis poisoning during hemodialysis, 2 had paroxysmal episodes and another demonstrated the early stages of the arrhythmia In nearly half the patients, therefore, digitalis intoxication assumed the form of paroxysmal atrial tachycardia with block In a study of electrocardiographic changes during 13 consecutive hemodialyses Kohn and Kiley[116] observed arrhythmias in 3 In 2 of these digitalis was implicated One patient, who sustained potassium extraction, showed increasing digitalis effect and then an atrial tachycardia In the other patient, in whom the potassium shift was small but other electro-

TABLE 6 *Causes of Paroxysmal Atrial Tachycardia with Block in 66 Episodes Occurring in 51 Patients.*

| PREDISPOSING FACTOR | NO OF PATIENTS | NO OF EPISODES | PERCENTAGE OF TOTAL EPISODES |
|---|---|---|---|
| Attack associated with digitalis | 39 | 54 | 81.8 |
| Overdose of digitalis | | 36 | 54.5 |
| Mercury diuresis and digitalis maintenance | | 8 | 12.0 |
| Miscellaneous factors and digitalis maintenance | | 10 | 15.3 |
| Renal potassium loss | | 4 | |
| Hemodialysis | | 2 | |
| Cortisone administration | | 1 | |
| Insulin administration | | 1 | |
| Calcium administration | | 1 | |
| Weight loss | | 1 | |
| Idiopathic attack | 12 | 12 | 18.2 |

lytes, including calcium, were corrected, a brief paroxysm of ventricular tachycardia developed Although the samples are small they indicate a much higher percentage of atrial arrhythmias than would be found in a random population with digitalis intoxication Since potassium depletion is becoming an increasing problem in patients with congestive heart failure a continuing rise in the incidence of paroxysmal atrial tachycardia with block is to be anticipated

*Prognosis* Patients in whom this arrhythmia is due to digitalis usually have serious heart disease All 5 patients with supraventricular tachycardia studied by Askey[117] died shortly after the inception of the arrhythmia In the series of 40 patients described by Decherd, Herrmann and Schwab[118] 55 per cent died during their hospital sojourn Of the 39 patients studied at the Peter Bent Brigham Hospital, 23 (60 per cent) died shortly after the onset of the tachycardia Perusal of the clinical records of the Brigham patients leaves little doubt that the high mortality was related to the continued administration of digitalis, at times in increasing doses Since paroxysmal atrial tachycardia with block is associated with ventricular rates of over 100, the tendency is to give more digitalis to slow the ventricles In the critically ill cardiac patient this usually induces more profound toxicity and eventually death

*Idiopathic paroxysmal atrial tachycardia with block* The 12 patients in whom the arrhythmia was idiopathic differed in a number of respects from those patients in whom it was due to digitalis[118] No etiologic agents or predisposing conditions were evident Six of the 12 patients had not received digitalis for

at least a month before the onset of the tachycardia. A digitalis effect was not present on the electrocardiogram, and only 1 patient manifested ventricular extrasystoles. Three had no demonstrable organic heart disease. The arrhythmia lasted in 6 of the 12 more than a month and in 3 for over a year. It had been present for nineteen years in 1 case and almost continuously for twenty-five years in another. In only 1 of the 39 cases due to digitalis had the paroxysmal tachycardia with block been present for longer than a month The mortality rate was significantly lower in the idiopathic group Two patients died (17 per cent), and in both death appeared unrelated to the atrial abnormality

Idiopathic paroxysmal tachycardia with block is a benign condition. When it occurs in young people it is compatible with a long, healthy and active life Digitalis therapy is not contraindicated if congestive heart failure is present. When a 1:1 response develops digitalis is the drug of choice for slowing the ventricular rate Pronestyl, potassium or quinidine is ineffective in restoring a normal sinus mechanism.

A convincing explanation of the mechanism that operates in idiopathic paroxysmal atrial tachycardia with block is lacking A basis for the pathogenesis of this arrhythmia may be an organic or functional defect in the atrioventricular conduction system The nervous mechanisms controlling heart rate are related to the effective cardiac output When the output is inadequate because of ventricular bradycardia, reflex atrial acceleration will follow Since only a fraction of atrial beats get through, rates in excess of 150 may be necessary to sustain output The persistence of the

atrial tachycardia when 1:1 conduction occurs following exercise or emotion may be due to the prolonged continuance of the rapid atrial rate, which conditions a new level of equilibrium of atrial muscle automaticity

There is another type of paroxysmal atrial tachycardia that is not related to digitalis When atrial fibrillation or flutter is being converted to sinus rhythm with quinidine a transition phase may develop that exhibits the features of tachycardia with block. This is a transient electrocardiographic pattern devoid of clinical significance

*Differentiation from other atrial mechanisms.* Paroxysmal atrial tachycardia with block may resemble nearly every atrial mechanism. Before the onset of block, when the atrial rate is slow and no previous tracings are available for comparison of P waves, it may be indistinguishable from a sinus tachycardia. When the rate exceeds 150 but the arrhythmia is still in a 1 1 response phase, it is usually considered as a supraventricular tachycardia This is clearly demonstrated in Figure 12 The patient, F G, whose underlying condition was a potassium-losing nephritis and malignant hypertension, had five episodes of tachycardia with block while on digitalis. The first bout (Fig 11) was precipitated by a mercurial diuret- [illegible]

rapid heart action with a rate of [illegible] She appeared critically ill with *palpitation extreme* anxiety and advancing pulmonary edema The electrocardio-

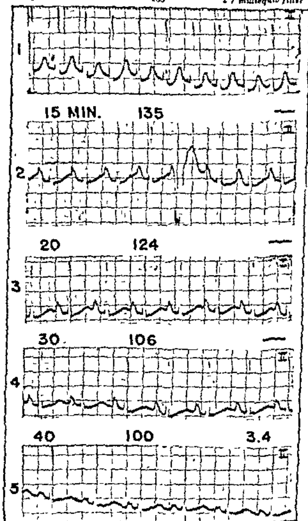



FIGURE 12 *Electrocardiograms in F G*

*On the basis of tracing (1) supraventricular tachycardia was diagnosed, and digitalis suggested However, the history of potassium-losing nephritis and previous episodes of paroxysmal atrial tachycardia with block suggested this was a 1 1 response phase of the latter arrhythmia Oral potassium was effective in rapidly restoring sinus rhythm*

graphic diagnosis of her arrhythmia was supraventricular tachycardia. Since the rhythm resembled a phase in the recession of paroxysmal atrial tachycardia with block, instead of digitalis she was given 20 milliequiv. of potassium chloride orally. Within fifteen minutes her heart rate dropped to 135, and within forty min-

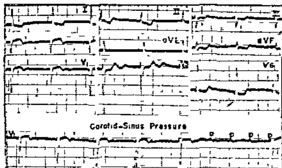



FIGURE 13 *Electrocardiograms in C W*

*For over a year the rhythm appeared regular on auscultation, and electrocardiograms were interpreted as showing nodal rhythm The perfectly iso-electric base line in all leads raised suspicion, however, of the underlying mechanism When carotid sinus pressure was applied while a V lead was being taken the presence of paroxysmal atrial tachycardia with block was revealed*

utes sinus rhythm was restored, with abatement of the signs of failure

When P waves are not in evidence in the standard or unipolar leads and the ventricular rate is slow because of atrioventricular block, nodal rhythm is the likely diagnosis Patient C W represents such a case of electrocardiographic misinterpretation (Fig 13).

This sixty-six-year-old man with rheumatic mitral and aortic disease had had atrial fibrillation for eleven years. *For more than a year the ventricular rhythm* had been perfectly regular on auscultation The electrocardiogram during this time was interpreted as showing nodal rhythm However, the application of carotid-sinus pressure, while a precordial lead was maintained in the $V_1$ position, revealed the true nature of the arrhythmia.

Atypical flutter is another name used by some for paroxysmal atrial tachycardia with block This is a misnomer, for it implies that the two mechanisms are nearly identical expressions of a common underlying process [45] Aside from important differences in pathogenesis and treatment there are significant electrocardiographic and clinical differences The patient in whom flutter develops is on the average a decade older than the one with tachycardia with block. He is less likely to have severe heart failure. He has not been on rigid salt restriction and has not received frequent mercurial injections before the onset of the rapid heart action. In flutter the atrial rate exceeds 250, except during quinidine administration; in paroxysmal atrial tachycardia with block it is invariably less The following electrocardiographic features further differentiate the two arrhythmias: in untreated flutter, atrioventricular block is usually 2·1, the Wenckebach type of conduction is rare; in nearly 70 per cent of the cases the P waves are inverted in Leads 2 and 3,[45] the base line between P waves is not iso-electric but has an undulant, sometimes see-saw quality, and ventricular premature beats are rare The prognosis in flutter is more favorable and

is about the same as that in the idiopathic variety of tachycardia with block.

Paroxysmal atrial tachycardia with block is at times confused with atrial fibrillation The diminutive P waves and changing degrees of atrioventricular block conduce to misinterpretation The development of tachycardia with block is not precluded by many years of chronic fibrillation Some of the cases of atrial fibrillation reported in the literature after digitalis overdosage may have been examples of paroxysmal atrial tachycardia with block Although atrial fibrillation is quite rare in patients with syphilitic heart disease, Resnik[198] observed 7 cases in which there appeared to be fibrillation due to digitalis intoxication It is to be noted that at the time of this report electrocardiograms were limited to three standard limb leads In these leads the two arrhythmias are frequently indistinguishable It is of interest that 2 of the patients at some time in the evolution of their fibrillation exhibited varying degrees of atrioventricular block In 1 patient 3 2 block occurred the first time digitalis was administered, this was followed by complete atrioventricular dissociation The second time digitalis was tried "atrial fibrillation" developed, lasting for twenty-six days and finally stopping six days after the discontinuation of strophanthin When a very small dose of digitalis was given a third time the drug induced "atrial flutter," the rate of the "flutter" being unusually slow, 165 The patient died the same day[198] It is therefore more than likely that some of the digitalis-induced "fibrillations" were actually instances of paroxysmal atrial tachycardia with block

When the ventricular rate of a patient with long-

standing fibrillation accelerates and regularizes after a diuresis or an increased dose of digitalis, tachycardia with block should be suspected. When the routine leads do not show this mechanism, exploration of the precordium with CR leads may demonstrate the blocked P waves Mild exercise may be helpful diagnostically. In the presence of fibrillation the irregularity will be increased; the converse is true in paroxysmal atrial tachycardia with block Carotid-sinus pressure may prove rewarding: it frequently enhances atrioventricular block, revealing the presence of nonconducted P waves Finally, if in a so-called case of fibrillation small ff waves are seen coming at a rate of about 200 per minute, paroxysmal atrial tachycardia should be suspected. Nevertheless, a significant number of cases remain in which identification of the mechanism is difficult. In such patients a test dose of potassium or a digitalis tolerance test may identify the arrhythmia

*Treatment*

The treatment of paroxysmal atrial tachycardia with block does not differ from the methods of managing other manifestations of digitalis intoxication Digitalis is stopped, and diuretic measures are suspended until all evidence of overdosage has disappeared The patient's activity is restricted To suppress toxicity either one of the salts of potassium or procaine amide (Pronestyl) is employed

*Potassium* The effectiveness of potassium salts has been pointed out A few comments are necessary on the indications for its use, methods of administration

and the hazards that attend therapy In the ambulatory patient with digitalis overdosage the daily administration of 5 0 to 7 5 gm. of potassium chloride in divided oral doses suffices for the control of intoxication This dose should be reduced or stopped after a therapeutic result has been achieved When the episode of intoxication is severe 5 0 gm of potassium chloride may be given at once This amount, when the compound is dissolved in a chilled fruit beverage, [illegible] In patients [illegible] develops 5 0 [illegible] ien given in divided daily doses on the day of, and the day after, the diuretic When acidosis is present the acetate or citrate salts of potassium can be used instead of the chloride Drastic depletion of this electrolyte should be avoided in the digitalized patient with uremia The elevated serum potassium level in these patients coexists with normal or reduced body stores

In a number of circumstances we prefer the intravenous route for potassium administration The advantages are that the action is prompt and results are certain, and when the electrocardiogram is continuously observed, it is safer than the oral route Once an oral dose is ingested one is committed to that dose When the potassium is given intravenously, however, the infusion is halted at the first evidence of peaking or tenting of the T wave,[110] and the hyperkalemia promptly disappears For intravenous use we employ a solution containing 40 milliequiv of potassium chloride in 500 cc of 5 per cent glucose and water This is given in the course of an hour and repeated if

necessary until a total dose of 120 milliequiv. has been given Once a therapeutic end point has been reached, oral maintenance is started.

We have given potassium *intravenously to the following types of cases:* first, to patients in shock due to ventricular tachycardia precipitated by digitalis or to patients exhibiting prefibrillatory ventricular rhythms that may result in sudden death; second, to elderly patients with heart failure and digitalis overdosage, since such patients are prone to develop poisoning even with small doses of potassium; third, to patients with paroxysmal atrial tachycardia with block, in order to prevent a prolonged 1:1 response phase that may aggravate the congestive heart failure; and fourth, when data were required to ascertain whether an abnormal cardiac mechanism was due to digitalis.

Should the cardiac patient in failure be maintained on small supplements of potassium? The release of myocardial potassium in failure, through the pathologic process itself as well as through the therapeutic methods now in vogue, appears to provide a rationale for such use. However, the loss of the cation in failure is in all likelihood a secondary expression of chronic lesions in intracellular physicochemical processes The liberation of potassium is therefore a component of the pathologic impairment, and replenishment of the accrued cellular deficits depends on correction of the [illegible]

lation of the levels in the extracellular compartment would be effective against a nearly *thirtyfold cellular*

concentration gradient To date there is no clinical evidence that long-continued administration modifies or benefits the course of congestive heart failure Furthermore, when appetite is normal, in the absence of renal or gastrointestinal potassium loss, the ubiquity of potassium assures an abundant supply of this cation

Potassium supplementation is indicated only in the presence of any of the serious manifestations of digitalis overdosage or when acute loss is superposed upon the chronic underlying disease Even under these circumstances the continued administration of large doses is hazardous It has been stated that in the absence of anuria the body can excrete large ingested amounts so rapidly that toxic levels cannot be produced [119,120] Other observers have found that ingested potassium may produce intoxication in patients with heart disease [121-124] Brown, Tanner and Hecht,[124] who gave 200 milliequiv (8 gm ) of potassium orally, reported striking differences between normal subjects and patients with congestive failure Although the peak serum level normally occurs within two hours of ingestion, in persons with heart failure it is reached within three hours, and the level is correlated with the degree of failure The serum level rose 26 per cent (to 5 5 milliequiv per liter) in normal persons, 43 per cent (to 6 0 milliequiv per liter) in patients with compensated heart failure and 67 per cent (to a value of 7 4 milliequiv per liter) in decompensated subjects Not only are these peaks reached later but they persist longer when the failure is uncontrolled In the patient without heart disease such a potassium load will be excreted within four hours, in the patient

with decompensation it may require twenty-four hours or longer. These differences are due to low renal clearances in patients with failure.[124]

In our experience the ingestion of even a lesser single dose of potassium may induce severe hyperkalemia This is especially true in elderly cardiac patients. Although they may have normal concentrating capacities and urea clearances they handle potassium as though afflicted with advanced renal impairment.

Since the hazards are real and the benefits are dubious routine administration of potassium should be restricted to cases in which its use is clearly indicated. It should be given in moderate doses with electrocardiographic supervision for the limited period of need.

*Procaine amide (Pronestyl).* A new agent, the *amide analogue of procaine, is proving effective in* controlling the arrhythmias due to overdoses of digitalis. For a number of years surgeons and anesthetists have employed procaine to control heart rhythm, especially during cardiac and thoracic surgery[199,200] The clinical use of procaine has been restricted because of rapid hydrolysis in the serum and a tendency to stimulate the central nervous system in the unanesthetized patient Procaine amide, unlike procaine, is stable within the body and in therapeutic doses is devoid of convulsant action To date, procaine amide is the most effective agent in protecting dogs under cyclopropane anesthesia from the arrhythmias caused by epinephrine[125]

The antiarrhythmic property of procaine amide resides principally in its ability to depress excitability[201]

t elevates the threshold to electric stimulation in all arts of the dog's heart Procaine amide also depresses onduction in both atria and ventricles and prolongs he absolute and relative refractory periods The de- ree of these changes is a function of the plasma level f the drug [201] Such quinidine-like effects are also oted in the turtle and human hearts [202,203] In con- rast to quinidine, however, myocardial contractility is ot depressed even with high concentrations of pro- aine amide [203]

Procaine amide is completely and rapidly absorbed rom the intestinal tract and can thus be given either rally or parenterally Peak levels after an oral dose re achieved in about ninety minutes [126] After intra- enous administration effects as assessed by the pro- ongation of the QT interval are noted within four minutes [127] The drug is slowly metabolized and ex- reted Plasma levels decline approximately 15 per ent an hour Roughly 60 per cent is excreted un- hanged in the urine On repeated oral doses a lateau is reached after thirty-six to forty-eight ours [126] The electrocardiographic effects, which re- emble those of procaine[128] or quinidine,[129] consist of PR and QT prolongation, T-wave flattening and QRS widening

The immediate hemodynamic effects of the intra- enous injection of procaine amide have been studied n 10 patients by cardiac catheterization [204] There vas a reduction in systemic and pulmonary artery ressure, with a prolongation of the mean circulation ime These values returned to control levels within bout thirty minutes In half this group of patients he cardiac output fell The hemodynamic changes

were related to the presence of heart disease and were least evident in patients with normal hearts

Procaine amide finds its most effective clinical application in the control of ventricular arrhythmias. It promptly abolishes most bouts of ventricular tachycardia and diminishes or eliminates ventricular premature beats.[127,132,205-207] In some cases it will control ventricular tachycardia when quinidine has been unsuccessful. The action of procaine amide on abnormal atrial mechanisms has been less spectacular In some cases recently established bouts of atrial fibrillation are reverted to sinus rhythm [130,132] Irrespective of whether such restoration is effected a slowing of the atrial rate follows. The ff waves become coarsened and widened and resemble flutter waves in their configuration. Procaine amide, like quinidine, exerts an atropine-like effect on the vagus nerve, with acceleration of the ventricular rate in the inadequately digitalized patient.[201] Procaine amide has been used with good results in nodal tachycardias, with variable results in supraventricular mechanisms and with little effect in most instances of flutter.

Many of the arrhythmias successfully treated with procaine amide have been precipitated by an overdose of digitalis [127 130] Stearns, Callahan and Ellis[207] were able to abolish by intravenous procaine amide nearly every arrhythmia due to digitalis. The doses ranged from 60 to 400 mg In 2 such patients with multiple ventricular extrasystoles the administration of procaine amide permitted the continuation of both digitalis and diuretic measures, with good effect.

The specific interaction between procaine amide and toxic doses of digitalis was experimentally studied

by Lown and Crocker,[131] who found that in dogs procaine amide was promptly effective in stopping ventricular tachycardias produced by an overdose of acetyl strophanthidin Such arrhythmias usually lasted from three to fifteen minutes. When 100 mg of procaine amide was given intravenously the tachycardia was abolished within a minute, without further recurrence of the tachycardia or ventricular extrasystoles

To test further the effect of procaine amide on the toxic threshold of digitalis in dogs the following study was carried out Dogs were digitalized with acetyl strophanthidin 5 successive times at two-hour intervals to an end point of ventricular tachycardia The first 2 digitalizations served as controls Before the remaining 3 digitalizations 100 mg of procaine amide was given intravenously (Table 7) In 38 control digitalizations in 7 dogs an average dose of 0 95 mg of acetyl strophanthidin was required to produce ventricular tachycardia After pretreatment with procaine amide the dose was increased to 1 69 mg. or 178 per cent of the control value When digitalization was carried out two hours after the administration of procaine amide the requirement of acetyl strophanthidin was still 37 per cent above the control level When small amounts of acetyl strophanthidin were injected just as an episode of ventricular tachycardia ended spontaneously there was an immediate resumption of the arrhythmia When procaine amide was used to stop such a bout of tachycardia, however, it was possible to administer nearly 65 per cent of the control dose of the drug before the abnormal mechanism was again induced (Table 7) [208]

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cessfully prevented the occurrence of ventricular tachycardia in 1 patient by the daily oral administration of 3.0 gm, he has been receiving procaine amide for two years without evident harm.

As experience is accumulating in the use of this drug, it is becoming clear that procaine amide frequently causes toxicity and may even cause death. Flushing of the face, giddiness, weakness, bad taste in the mouth, thirst, apprehension, nausea and vomiting are some of the milder reactions[207] Febrile episodes,[209,210] allergic reactions[127,211,212] and agranulocytosis with fatal outcome[213,214] have been described. The most common untoward reaction with intravenous use is hypotension Significant lowering in systolic and diastolic pressures, which forced discontinuation of therapy, was observed in 40 per cent of the patients treated by Stearns, Callahan and Ellis[207] While the rate of infusion may be a factor, it occurs with all dosage schedules and may follow an injection rate of 25 mg per minute[207] Intraventricular conduction disturbance is a common manifestation In some instances of ventricular tachycardia, it may accelerate the ventricular rate and induce prefibrillatory rhythms[215] Sudden death after a total intravenous dose of 300 mg has been reported[216] Procaine amide is prone to induce ventricular fibrillation in patients with complete atrioventricular dissociation[215] It is also contraindicated in patients with asthma[207] The elderly patient with advanced cardiac failure is more susceptible to the toxic side effects, especially with intravenous use In such patients the drug should be given orally

Procaine amide is an important adjunct to the

management of the arrhythmias due to an overdose of digitalis. It resembles potassium in its effect. Its action may be due to alteration in membrane permeability, facilitating the entry of potassium into the cell.

# CHAPTER VII

## A Digitalis Tolerance Test

The problem of how to digitalize, how much drug to use and when to use it dates to Withering. The studies of Eggleston[133] provided a rational approach to digitalization and indicated that the quantity of drug required is a function of body weight. In practice, however, the high incidence of both overdigitalization and underdigitalization, when the weight formula was rigidly applied, led to the recognition that the dose of digitalis for maximum therapeutic effect cannot be predicted in advance but must be derived for each patient in the trial-and-error process of digitalization. Although empiric dosage determinations suffice for the majority there are increasing numbers of cases in which even fractional digitalization is fraught with danger.

At times the very question of administering more digitalis is uncertain. Will additional digitalis aggravate or improve failure? Are the symptoms of nausea and vomiting due to overdosage or to advanced decompensation? Are ventricular premature beats indexes of toxicity or evidence of myocardial anoxia from increasing failure? Is an episode of paroxysmal rapid heart action an expression of too much digitalis or an indication for more? These and similar questions frequently confound the clinician and are conducive to indecision and contradictory half measures. The following experience illustrates one of the problems mentioned:

M O , a 36-year-old woman, manifested ventricular tachycardia and peripheral vascular collapse 48 hours after a mitral valvuloplasty She had been on maintenance digitalis therapy, and her previous rhythm had been that of atrial fibrillation The cause of the tachycardia was uncertain She was treated with large doses of procaine amide, followed by intravenous injection of quinidine and potassium chloride, without reversion These measures further aggravated the ventricular tachycardia by accelerating the rate, increasing intraventricular block and establishing multifocal sites for the arrhythmia (Fig 14) The ineffectiveness of both procaine amide and potassium indicated that digitalis was not a factor in the ventricular tachycardia It was suggested that decompensation with impaired coronary perfusion and resulting myocardial anoxia stimulated an irritable myocardial focus produced by the trauma of valvuloplasty and thus precipitated the ectopic rhythm If the initiating factor was increasing failure, digitalis, by restoring compensation, would prove effective where other measures failed She was therefore given small amounts of ouabain (0 1 mg ) every 30 minutes (Fig 14) After a dose of 0 3 mg atrial fibrillation emerged as the dominant rhythm After another 0 3 mg all evidence of ventricular irritability had disappeared The patient however, died 24 hours later

Ventricular tachycardia is regarded as one condition in which digitalis is absolutely contraindicated In this patient digitalis was effective in reversing the arrhythmia If there had been a method for determining the digitalis status and rapidly effecting digitalization, death might have been prevented

We have seen a number of similar cases in which, in retrospect, it seemed likely that if digitalis had been given promptly and in adequate dosage, the irreversible failure or tachycardia might have been controlled The converse has also been our experience digitalis was given, with harmful consequences, and in retrospect it appeared that the patient's deterioration in the first place was due to overdosage The problem is therefore one of evolving a method for de-

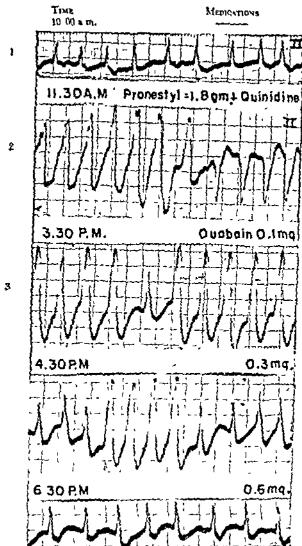



FIGURE 14 *Ventricular Tachycardia Following Mitral Valvuloplasty in a Patient on Maintenance Digitalis*

*Procaine amide, quinidine and potassium chloride were administered intravenously without effect Ouabain caused reversion to atrial fibrillation*

termining rapidly and without excessive hazard the patient's digitalis status and requirements. We have devised a test that provides such information. Before delineating the method and its clinical use other approaches to the problem will be briefly reviewed.

*Electrocardiogram as Indicator of Digitalization*

When Cohn, Fraser and Jamieson[217] first reported that digitalis caused a characteristic alteration in the form of the T wave, it was hoped that the electrocardiogram would provide information on the degree of digitalization Pardee suggested that the T wave might be used as a measure of digitalis action in man[218] Other correlative studies then followed. Bromer and Blumgart[219] found that the earliest alteration of the T wave occurred when about 50 per cent of the total therapeutic dose had been ingested They concluded that T-wave changes served as a quantitative index of the amount of digitalis present in the body It was also reported that QT shortening might be employed as a measure of digitalization[220,221] Some investigators even suggested that the electrocardiographic changes were not only specific for digitalis but were characteristic for each type of digitalis preparation employed[141,222,223]

Contrary viewpoints were also expressed Geiger and co-workers[224] found that in digitalized patients the electrocardiographic changes were neither uniform nor consistent When progressive digitalization was studied by serial electrocardiograms no quantitative correlation was observed between the amount of drug and the resultant changes in the ST segment and T-wave contour Gold and his group,[225] in attempting to

evolve an electrocardiographic method for the bio-assay of digitalis preparations, found that carefully selected normal subjects at rest were required to give a satisfactory dosage-response curve

The ST segments and T waves are highly variable parameters of the electrocardiogram. They are affected by alteration of body position, exercise, temperature, infection, excitement, hyperventilation, electrolytes and a host of other factors Myocardial injury and ventricular hypertrophy give patterns frequently indistinguishable from those due to digitalis It has already been pointed out that advanced poisoning may occur without the tell-tale electrocardiographic effects of digitalis The conclusion to be drawn is that in the absence of intoxication, the electrocardiogram is without value in assessing the degree of digitalization in the cardiac patient. At best it may suggest the presence of digitalis in the body

*Chemical and Biologic Assay Methods*

Until very recently there was no reliable microchemical method for detecting digitalis and its glycosides in the minute quantities that are active biologically Chemical determinations were a thousandfold less sensitive than the tissue concentration at which the drug is effective The earliest chemical study was that of Keller and Killiani [226] The presence of digitalis was ascertained by the formation of a blue ring characteristic of digitoxose at the interphase of test fluid and sulfuric acid The test was capable of detecting up to 0 05 mg of digitoxin A more sensitive determination depended on the red color formed by the interaction between the unsaturated lactone ring

of digitoxin and alkaline dinitrophenol.[227] The biochemical studies of the digitalis content of body fluids were complex and cumbersome, and the results were not reproducible [228]

The absence of a suitable chemical test led to the use of animal hearts for the bio-assay of digitalis [229-231] At first, intact animals such as frogs, guinea pigs and cats were employed as test objects The determination was based on the production of cardiac standstill in a prescribed time [232-234] The use of the isolated frog heart or the heart-lung preparation, and recently the cat's papillary muscle, enhanced sensitivity of detection.[15 235 236] A still more sensitive test object was provided by the embryonic chick heart [237 238] The heart was immersed in the test fluid containing digitalis, and the concentration was judged by the production of cardiac irregularities

*Embryonic duck-heart micro-assay method.* An approach similar to the chick-heart method was employed by Friedman, Bine and co-workers,[239] who adapted the embryonic duck heart for the bio-assay of digitoxin They were able to detect concentrations as low as 0 05 microgram per gram of tissue Would this test permit evaluation of the digitalized state? Before answering the question it is necessary to review briefly some of the findings of these and other investigators concerning the distribution and concentration of digitalis in the animal body [240-244]

Digitoxin is completely absorbed from the intestinal tract Absorption is not impaired by the presence of right-sided failure [243] Once digitoxin enters the blood a considerable fraction is physically bound to plasma albumin [245-249] Three minutes after intravenous ad-

Unlike other mammals, which did not excrete significant amounts of digitoxin, man eliminated through the kidney from 40 to 50 per cent of a single dose as cardiac glycoside.[243,260,261] This elimination occurred at a rate of 5 per cent of the administered dose during the first twenty-four hours and lesser amounts thereafter. [illegible]

the urine It has been accordingly postulated that the state of complete digitalization is characterized by a daily excretion of 30 to 50 micrograms (0 03 to 0 05 mg ) of digitoxin [243] The presence of acute left-sided failure or chronic decompensation did not diminish renal excretion During the first twenty-four hours after the onset of acute right-sided failure, excretion decreased about 50 per cent and thereafter reached control values

Increases in renal excretion of digitoxin occurred consistently in patients with subjective or objective symptoms of overdosage Patients with digitalis intoxication excreted about twice as much in twenty-four hours as the compensated cardiac patient The embryonic duck-heart preparation has been used in difficult cases to determine whether adequate or excessive digitalization existed [244]

The duck-heart preparation provides a valuable method for investigating the metabolism of digitalis It has limited applicability, however, in assessing the clinical state of digitalization The test is complex, time-consuming and requires special facilities It shares with other bio-assay technics the disadvantage of excluding substances which might adversely affect the

embryonic heart This necessitates a cumbersome chemical process of extraction of the digitalis agent Furthermore, in order to overcome the extreme variation which characterizes biologic testing, 5 or more hearts have to be employed for each determination. This apparently does not assure consistency of results, for Friedman and co-workers[253] had to employ eggs derived *from a single hatchery* which has maintained a thoroughbred strain for over two decades. A fundamental objection to such an approach, rather than

tibility of the myocardium to digitalis Such data are critical for correct clinical evaluation

*Radioactive digitalis* With the development of radioisotope technics, reversion to the chemical method of studying the metabolism of digitalis has become possible

The biosynthesis of radioactive digitalis has been achieved through exposure of digitalis purpurea plants to an atmosphere of radioactive carbon dioxide[262] The tracer technic permits great sensitivity for detecting minute amounts of labeled drug, it is possible to assay as little as 0 02 microgram of radioactive digitoxin This method can be adapted to follow metabolic products of the parent compound by distinguishing between unchanged digitoxin and other cardioactive principles[263] In 1950 Geiling and co-workers,[262] utilizing this technic, reported that dogs excreted up to 46 per cent of a single dose of digitoxin in the urine. Fischer and associates[264] found that cats and rats eliminate a nearly similar amount of unchanged digitoxin and metabolites through the urinary route.

The finding of the importance of the kidney as a major pathway for elimination of digitalis and its breakdown products contradicts the results of earlier investigations[256-258,265,266] but agrees with the duck-heart method. When digitoxin labeled with radioactive carbon is administered to cardiac patients, 60 to 80 per cent is eliminated by the kidneys either as unchanged digitoxin or as its metabolic derivatives.[262] After a single intravenous dose there is a marked initial excretion of digitoxin lasting for two days; this is followed by a gradual leveling off after the fifth day. During the initial three-day period 20 per cent of the administered dose is eliminated, and about half this amount is excreted in the first twenty-four hours

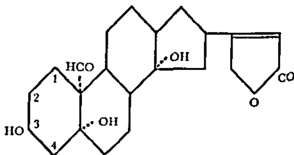
Most of the carbon-14 from the labeled drug is excreted as metabolic products Only 6 to 10 per cent of the original drug is eliminated as unchanged digitoxin, and this occurs mainly in the first six hours after injection. A minute amount of unchanged digitoxin can be detected in the urine for as long as forty days after administration, and carbon-14 products continue to be present in the urine up to the seventy-fourth day[263] The cumulative effect of digitoxin appears to be related to its persistence in the body The significance of these radioactive metabolites is uncertain Their high specific activity suggests direct derivation from digitoxin rather than resynthesis from the bodily carbon dioxide pool, where some of the carbon-14 enters

It is conceivable that tracer technics may be adapted for clinical use to assess bodily disposition of digitalis By giving radioactive digitalis and determining urinary excretion and specific activity over the myocar-

dium the digitalis status may be delineated At present these methods are not of practical significance for the patient with congestive heart failure.

*Acetyl Strophanthidin Tolerance Test*

*Principle.* The purpose of the test is to ascertain the degree of digitalization and myocardial sensitivity to digitalis in patients whose digitalis status is in doubt. Since there is currently no clinical method for determining cardiac susceptibility to digitalis, except through the act of digitalization, such a procedure is employed. Acetyl strophanthidin, the agent used, has a short latency, peak effect is achieved in the course




*Strophanthidin*

of several minutes, and dissipation is rapid The amount of drug necessary for a therapeutic or toxic end point determines whether digitalis is to be used and the approximate dosage for optimal effect

*Agent* Acetyl strophanthidin is an ultrarapid-acting synthetic ester of the cardiac aglycone, strophanthidin. It has been proved possible to introduce various radi-

*cals on the steroid-ring system of the strophanthidin* molecule by utilizing the highly reactive properties of the secondary hydroxyl group at the carbon-atom 3 position. Several derivatives of strophanthidin have been prepared by interaction with various acids and glucose molecules [267,268]

Wedd and Blair[269] recently cast doubt on the digitalis-like properties of this agent. They found that acetyl strophanthidin failed to shorten the refractory period, interpreted as the QT interval, without impairing contractility Since digitalis glycosides shorten the QT interval, they concluded that acetyl strophanthidin is not a digitalis-like substance and that its therapeutic action is due to vagus-nerve stimulation Greiner and Reilly,[270] however, convincingly demonstrated the digitalis-like properties of this drug When hypodynamic papillary muscles of cats' hearts were exposed to acetyl strophanthidin there was a marked increase in the force of contraction The response was qualitatively similar to that with other digitalis bodies, but quantitatively this drug was the most powerful of all the preparations tested Although the relation between the electric activity and therapeutic action of digitalis is not clear, it is likely that the critical properties that distinguish the digitalis drugs are due to positive inotropic action on the myocardium

In tests on human subjects acetyl strophanthidin has been found to be a potent digitalis-like agent [134 136] It is much more rapid in effect and dissipation than ouabain, generally conceded as the most rapid-acting of all cardiac glycosides [135,137-140] A comparison of some of the clinical properties of the two drugs is presented in Table 8 The earliest effect of acetyl

strophanthidin, during 154 trials in 125 patients, occurred within one to five minutes, with an average of three and a half minutes [136] In a number of patients we have observed an effect as early as thirty *seconds after administration.*[140] When the drug was given over a five-minute period 70 per cent of the maximum action, as gauged by the slowing of the ventricular rate of atrial fibrillation, was evident at the end of injection.[135] The effect persisted for about an hour, and in no case was it present after four hours.[136] In dogs it is possible to digitalize at two-hour

TABLE 8 *Comparison of Speed of Action and Dissipation of Ouabain and Acetyl Strophanthidin* *

| DRUG | EARLIEST EFFECT | PEAK ACTION | PERSISTENCE OF EFFECT | DURATION OF TOXICITY |
|---|---|---|---|---|
| | *min* | *min* | | |
| Ouabain | 5-20 | 60-120 | 3 hr -5 days | Several hr |
| Acetyl strophanthidin | ½-5 | 12 | 2 hr | 30 min |

*Note that action of acetyl strophanthidin is more rapid and more transient than that of ouabain

intervals without evidence of cumulation.[140] Toxicity lasts for about thirty minutes. Enselberg and his coworkers,[136] who have had the most extensive clinical experience with this agent, reported toxicity in a quarter of the trials However, they gave the whole digitalizing dose at once. In experiments on both dogs and human beings acetyl strophanthidin is about half as potent as ouabain—that is, 0 1 mg of ouabain is equivalent to 0 2 mg. of acetyl strophanthidin [135,140]

*Animal experiments.* A number of problems re-

mained to be solved before the application of acetyl strophanthidin as a testing agent in man: the development of methods for eliminating or controlling toxicity; determination of whether the action of acetyl strophanthidin on the heart is quantitatively additive to that of any other digitalis preparation already in the body—the critical point of the tolerance test; and ascertaining of whether the state of prior

TABLE 9. *Summary of Ouabain Assay with Acetyl Strophanthidin in 4 Dogs*

| No of Assays | Deviation in Predicted Dose of Ouabain from Amount Given | Duration of Toxicity | |
|---|---|---|---|
| | | Acetyl strophanthidin | Acetyl strophanthidin and ouabain |
| | % | min | min |
| 20 | 13 | 6 | 8 |

digitalization modifies the toxic pattern of acetyl strophanthidin either in quality or in duration

These problems were studied in dogs It was found that administration of small increments of acetyl strophanthidin at brief intervals produced significant slowing or rare extrasystoles without serious toxicity If toxicity was precipitated intravenous injection of procaine amide was also immediately effective in abolishing the arrhythmias [131] When ouabain was present in the body the additional administration of acetyl strophanthidin to the point of toxicity did not alter the toxic pattern or prolong its duration (Table 9)

The possibility of determining the quantity of digi-

talis in the body by means of acetyl strophanthidin was tested in dogs When acetyl strophanthidin is given at two-hour intervals the dose for the production of ventricular tachycardia remains constant. If, however, a dose of ouabain is administered between successive doses of acetyl strophanthidin, there is a reduction in the dose of acetyl strophanthidin equivalent to the amount of ouabain given A typical example, one of a group of identical experiments, is presented in Figure 15. Four doses of acetyl strophanthidin

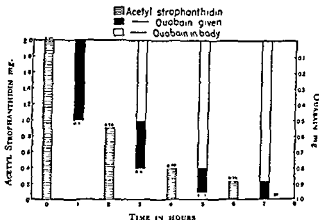



**Figure 15** *Declining Doses of Acetyl Strophanthidin for the Production of Ventricular Tachycardia When Increasing Amounts of Ouabain Accumulate in the Body*

were given to the same toxic end point two hours apart The first time the dose required was slightly in excess of 2 0 mg When acetyl strophanthidin was again given, but this time preceded by 0 5 mg of ouabain administered an hour earlier, it required

only 50 per cent of the first digitalizing dose to produce ventricular tachycardia Each time ouabain was injected the reduction in the dose of acetyl strophanthidin for toxicity was nearly equivalent to the amount of ouabain administered The over-all results in 20 similar assays are shown in Table 9 The average deviation in the predicted amount of ouabain from the amount actually given was 13 per cent This was the same as the magnitude of deviation in successive digitalizations with acetyl strophanthidin when no ouabain was given This method permits accurate appraisal of the quantity of a digitalis preparation present within the body With these preliminary observations it was considered justified to employ the acetyl strophanthidin tolerance test in man

## *Clinical Studies with the Tolerance Test*

*Material and methods* The test was employed in patients with congestive heart failure whose digitalis status was in doubt or in whom myocardial sensitivity to the drug was believed to be increased To date 20 tests have been carried out in 18 patients the majority of whom were critically or terminally ill [140]

*Technic* The procedure of the test was quite simple Two ampoules, each containing 0 6 mg of acetyl strophanthidin, were diluted to 20 cc in 5 per cent glucose and water If the patient to be tested had received little or no digitalis 0 3 mg of acetyl strophanthidin (or 5 cc of the dilution) was given intravenously every five minutes until the achievement of either a therapeutic effect or a mild toxic response In the presence of possible digitalis intoxication the schedule was modified Either the interval

between doses was increased to ten minutes or the initial two increments of acetyl strophanthidin were reduced to 0.15 mg. In the presence of an arrhythmia that was most probably due to digitalis potassium was first given and, if ineffective, followed by a tolerance test. The electrocardiogram was continuously observed during the test. One-minute strips were taken before each injection. With the onset of evidence of intoxication, nausea excepted, the test was stopped. If the toxic pattern consisted of ventricular premature beats small amounts of procaine amide were given intravenously until all extrasystoles had disappeared.

*Interpretation* Interpretation of the test was based on the amount of acetyl strophanthidin required and on the patient's qualitative response If toxicity developed after the first injection of 0.15 mg. or 0 3 mg overdosage was presumed to be present, and no further digitalis was administered. If toxicity ensued after 0.6 mg without the intervention of any therapeutic effect the patient was regarded as adequately digitalized When therapeutic action occurred after 0 6 mg or 0 9 mg fractional doses of any one of the commonly used digitalis preparations were given until the same effect had been achieved If the patient required 1 2 mg or more full digitalization was carried out.

*Results* In 18 of the 20 tolerance tests the information provided served as an immediate and accurate guide to further therapy The results were uncertain in 1, and another patient died soon after the completion of a test Twelve of the tests indicated that the patients could profit from more digitalis either in full or partial dosage, and seven of the tests were inter-

preted as contraindicating digitalis (Table 10). Although the findings of the tolerance test frequently contraindicated clinical impressions, the patients' subsequent courses corroborated the conclusions of the test in all instances

*Patients requiring digitalis.* Of the 12 patients re-

TABLE 10 *Results of 20 Assays in 18 Patients.*

| DIGITALIS REQUIRED | NO OF ASSAYS | DIGITALIS NOT REQUIRED | NO OF ASSAYS | EFFECT UNCERTAIN |
|---|---|---|---|---|
| Full digitalization | 8 | Toxicity | 3 | |
| Partial digitalization | 4 | Full digitalization | 2 | |
| | | Increased sensitivity | 1 | |
| | | No therapeutic effect | 1 | |
| Totals | 12 | | 7 | 1* |

*Patient exhibited bidirectional ventricular tachycardia before test.

quiring digitalis 9 were on maintenance doses Two had received no digitalis and it was uncertain whether 1 had taken any Some of these cases are reported below

C C, a 54-year-old man with hypertensive cardiovascular and coronary-artery disease, had sustained 2 episodes of myocardial infarction before entering the hospital After his 2d infarct right-sided and left-sided failure developed He was therefore [illegible] leaf and main-

[illegible] He also

[illegible] h before

[illegible] He had

[illegible] marked

[illegible] hycardia

[illegible]

phanthidin every 10 minutes After 1.2 mg he began t
vomit again At this point the heart rate had decrease
about 20 per cent, and the extrasystoles had disappeare
(Fig 16) The test was interpreted to denote that h
needed full digitalization. Within the next 96 hours, h
received 4.0 mg of Digoxin This dose controlled his fail
ure and further slowed his rate

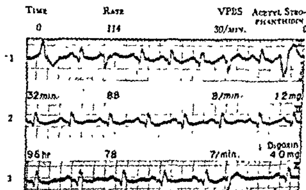



Figure 16 Tracings in C C

*The acetyl strophanthidin tolerance test indicated the need of full digitalization. When this had been accomplished failure was controlled, and extrasystoles diminished*

Without an acetyl strophanthidin tolerance test there appeared to be no way of determining this patient's digitalis needs The nausea, vomiting and multifocal ventricular extrasystoles suggested overdosage and urged discontinuation of the drug. The unfavorable course, the increasing pulmonary and hepatic congestion and the background of myocardial infarction intimated that a possible basis for the

clinical picture was increasing failure that might be remedied by more digitalis Even though it was concluded that he needed more digitalis, the amount required would have remained uncertain and inadequate dosage might have vitiated effective action The therapy during the month before hospitalization was characterized by vacillation between half measures and resulted in sapping of the patient's wellbeing and the physician's morale.

G G, a 49-year-old man, had syphilitic aortic insufficiency Twelve hours before admission dizziness, marked weakness, dyspnea and palpitation developed A supraventricular, tachycardia with a rate of 180 was found to be the cause of his symptoms Sedation, carotid-sinus pressure and Prostig- [illegible]

rate thereupon slowed, and there was an abrupt reversion to sinus rhythm At this point he exhibited 2d-degree heart block, a changing pacemaker and ventricular premature beats Intravenous injection of procaine amide in a dose of 300 mg controlled these manifestations

The tolerance test is not only a diagnostic procedure but also, in some cases, a therapeutic measure Reversion of supraventricular tachycardias requires a digitalis preparation that has short latency, prompt peak action and rapid dissipation of toxicity, acetyl strophanthidin has these properties Enselberg and his co-workers[156] caused 11 of 12 cases of supraventricular tachycardia to revert to sinus rhythm with acetyl strophanthidin, the majority within one to three minutes In 1 refractory case the patient had "auricular tachycardia with high degree atrioventricular block"

In patient G.G. the onset and progress of pulmonary edema due to the rapid heart action demanded prompt digitalization. Since he had received some

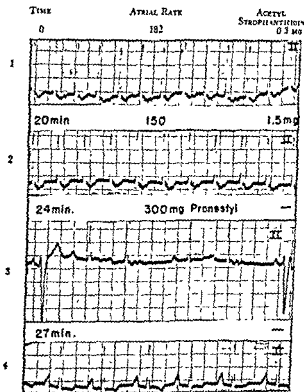



FIGURE 17 *Electrocardiograms in G.G., Showing that Acetyl Strophanthidin Caused the Arrhythmia to Revert to Sinus Rhythm.*

digitalis the amount to be given was uncertain. If ouabain had been used the equivalent dosage would

have been 0 7 mg. to 0 8 mg. This dose could not have been administered with safety in less than two or three hours, and the longer period might have jeopardized the patient's life. The problem with some *cases of supraventricular tachycardia is that a toxic* amount of digitalis may be necessary for reversion, *as in this patient. When toxicity develops before the* arrhythmia is controlled it is hazardous to continue with more digitalis Furthermore, the toxic reaction may be more serious and prolonged than the initial arrhythmia These difficulties are either lacking or at a minimum when acetyl strophanthidin is used

A N (whose history was presented on page 67) had severe right-sided and left-sided failure, a nodal tachycardia and ventricular premature beats at the time of hospitalization for mitral-valve surgery After digitalis had been stopped the rhythm reverted to atrial fibrillation, but he continued to have premature beats and runs of regular ventricular rhythm His condition had by this time deteriorated, and he was regarded as terminally ill The consensus was that he was [illegible]

In this patient clinical judgment was contradicted by the results of the tolerance test No basis existed before the test for assuming that he required full digitalization All therapeutic measures were ineffective in controlling his advancing failure, and it was expected that he would die within a few days The proper

use of digitalis not only improved his status but also permitted him to be operated on

The experience of patients requiring partial digitalization is illustrated in A N, and in G R (p 128)

After the valvuloplasty A N exhibited marked sensitivity to both overdigitalization and digitalis inadequacy In both circumstances a nodal tachycardia, with aggravation of the

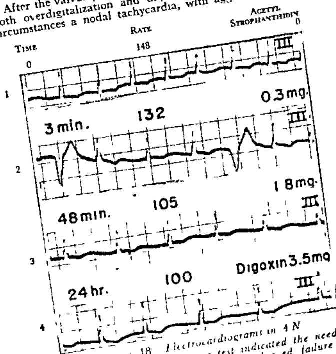



FIGURE 18 *Electrocardiograms in A N Acetyl strophanthidin tolerance test indicated the need for full digitalization When this was achieved failure was controlled*

failure developed Immediately after operation he had a nodal tachycardia which was due to overdosage and was corrected by the intravenous administration of potassium

(See Fig 6) When digitalis was stopped for a few days a nodal tachycardia again developed Because electrocardiographically it appeared to be identical to the previous arrhythmia, notwithstanding the fact that he was off digitalis the tachycardia was again ascribed to digitalis intoxication The intravenous administration of 35 milliequiv of potassium chloride was ineffective (Fig 19) An acetyl tolerance

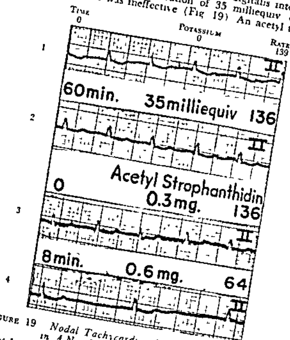



FIGURE 19 *Nodal Tachycardia after Mitral Valvuloplasty in A N—Not Helped by Potassium*

*Acetyl strophanthidin tolerance test indicated the need for more digitalis*

test was carried out Within 8 minutes after a total dose of 0 6 mg the rate dropped precipitously from 136 to 64 per minute, and was maintained there by 1 mg of Digoxin

In this case identical electrocardiographic arrhythmias were caused by diametrically opposite conditions, and a correct appraisal required the use of both potassium and acetyl strophanthidin.

G R, a 32-year-old woman with rheumatic mitral stenosis and atrial fibrillation, entered the hospital as an emergency admission to the surgical service. Four hours earlier she had experienced sudden, severe pain and numbness in the right leg She was anxious, sweating profusely and complaining of dyspnea, palpitation and pain in the right limb
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ate p
howe
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maintenance digitalis for 3 years, 2 days before hospitalization her daily digitoxin dose was increased to 0 2 mg Since she had some ventricular premature beats, a tendency to regularity in the fibrillation and what appeared to be P waves in Lead $V_1$ the possibility of digitalis overdosage was considered An acetyl strophanthidin tolerance test was carried out She received 0 3 mg of the drug every 10 minutes (Fig 20) After 0 6 mg there was a material reduction in heart rate, and she experienced nausea She was then given 0 5 mg of Digoxin intravenously and taken to the operating room Her rate did not rise over 100, and a successful embolectomy was performed

In this patient the test again provided diagnostic information and proved of therapeutic value. The rapid heart rate was precipitated by the peripheral embolization The daily digitalis intake, sufficient for usual needs, was inadequate in this emergency. A small increment of drug controlled the tachycardia; thereafter, the digitalis needs receded to the former level of requirement The special value of acetyl strophanthidin in this case was the rapidity of its effective action Within twenty minutes the patient was prepared for operation

sidered. An acetyl tolerance test was carried out. After the first 0 3 mg there was a change in atrial pacemaker and a slight acceleration of rate. This was not noted at the

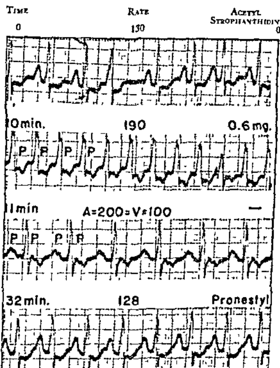



Figure 21 *Electrocardiograms in R T*
*Tolerance test induced paroxysmal atrial tachycardia with block, which was controlled with procaine amide Digitalis was not considered indicated*

time and another 0 3 mg was given Paroxysmal atrial tachycardia with block resulted (Fig 9) This reverted to a sinus tachycardia on the intravenous injection of 750 mg of

procaine amide (Fig 21) It was concluded that the patient had had adequate digitalis and was bordering on intoxication The sinus tachycardia was the result of failure and could not be controlled until the failure was abolished She was given much sedation and morphine. Within a few hours the pulmonary edema began to abate, and a reduction rate followed She recovered, and some days later a mitral valvuloplasty restored her nearly to full activity

A long-acting digitalis preparation might have prolonged the toxic response, and the pulmonary edema might have impeded or prevented restoration of compensation Within a few minutes, through use of the tolerance test, it was evident that digitalis was not to be employed

*Uncertain and unfavorable results* In 1 patient the results were uncertain The patient came in with left-sided failure and atrial fibrillation with a ventricular rate of 160 A dose of 1 6 mg of Cedilanid intravenously did not slow the rate The next day he experienced a cerebrovascular accident, with frequent grand-mal seizures During the convulsion he had bidirectional ventricular tachycardia To ascertain whether digitalis would slow the rapid fibrillation acetyl strophanthidin was given However, the sporadic recurrence of bidirectional ventricular tachycardia prevented judgment whether the patient was underdigitalized or overdigitalized

Acetyl strophanthidin accelerated the death of another patient, who was terminally ill with left-sided and right-sided failure unresponsive to all measures While she was on maintenance digitalis an episode of rapid heart action interpreted as supraventricular tachycardia with left-bundle-branch block developed The arrhythmia was terminated with procaine amide

Two days later, because of a ventricular rate of 120, it was decided to carry out a tolerance test. Within thirty seconds of the injection of 0 3 mg of acetyl strophanthidin multifocal ventricular premature beats developed, and within a minute progressed to ventricular tachycardia. It was now evident that the previous arrhythmia had also been an episode of ventricular tachycardia. The cerebral symptoms, the anorexia and *the extreme regularity of the atrial* fibrillation appeared as the obvious stigmas of advanced digitalis intoxication She was therefore given 200 mg of procaine amide intravenously, with reversion to rapid and regular fibrillation However, about nine minutes after the acetyl strophanthidin and six minutes after the procaine amide she grew cyanotic, with gasping respiration The electrocardiogram revealed ventricular fibrillation.

Whether the terminal episode was due to acetyl strophanthidin, procaine amide or other factors will never be established with finality. Deaths after small intravenous doses of procaine amide have been reported [130] The chain of circumstances in this patient demands that her death be ascribed to the tolerance test *It seems to us that a number of errors of judgment were committed in this case* In the first place the initial arrhythmia was not recognized as ventricular tachycardia Secondly, the symptoms, as well as the regular and rapid ventricular response in a patient with atrial fibrillation, should have indicated that she was still seriously intoxicated at the time of the test. In the presence of overt digitalis intoxication the administration of potassium is the procedure of choice. Without the tolerance test it is likely that the patient

would have received more digitalis and probably the outcome would have been identical.

*Discussion*

The *amelioration of disease by therapeutic means* that alter internal biologic processes carries with it the constant possibility of injury In deciding the justification of any new drug or procedure one must weigh the benefits to be accrued against the hazards to be encountered in relation to the seriousness of the underlying problem In the treatment of advanced cardiac disease situations in which the patient's well-being depends on an accurate appraisal of digitalis needs frequently arise No method has been available to date for this purpose The test outlined above provides an indication whether digitalis can be safely given or must be withheld Our experience has impressed us with both its great value and its potential danger Its use is justified only in the most carefully selected cases There must be real doubt concerning the digitalis requirements that cannot be resolved by simpler clinical means before the test is employed

# CHAPTER VIII

## Conclusions

In recent years a great deal of new information has accumulated on the mode of action of digitalis and on its benefits and dangers in the treatment of congestive heart failure

Of clinical importance is the recognition of the existing relation between digitalis and potassium. Depletion of body potassium lowers the myocardial threshold to the toxic action of digitalis This finding is especially significant today when the management of heart failure is based in large measure on the manipulation of electrolytes that is attended by loss of body potassium It is likely that the altered treatment of heart failure contributes to the rising incidence of digitalis intoxication.

Digitalis overdosage affects atria as well as ventricles In the former it gives rise to a specific arrhythmia, paroxysmal tachycardia with block, which is readily controlled by the salts of potassium or procaine amide

The variation of the response of the heart to digitalis in any one patient, the frequency of conditions in which underdigitalization and overdigitalization are indistinguishable and the similarity of paroxysmal atrial tachycardia with block to many nondigitalis-induced arrhythmias have made necessary a procedure for providing information on the digitalis status of the cardiac patient A digitalis tolerance test that provides

such data has been devised It is based on a biologic assay of myocardial sensitivity to an ultrarapid-acting, digitalis-like drug, acetyl strophanthidin

The newer methodologies employed, including cardiac and coronary-sinus catheterization, renal hemodialysis, micro-assay of digitoxin with the embryonic duck-heart preparation and radioactive digitalis compounds, promise a further extension of knowledge concerning the mechanism of heart failure and the mode of action of digitalis.

The introductory words of Withering to his treatise, which ushered in a new era in the care of patients with congestive heart failure, form an apt conclusion to our study:

> These remarks consist partly of matter of fact and partly of opinion The former will be permanent, the latter must vary with the detection of error or improvement of knowledge I hazard them with diffidence and hope they will be examined with candor not by contrast with other opinions but by an attentive comparison of the phenomena of disease

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